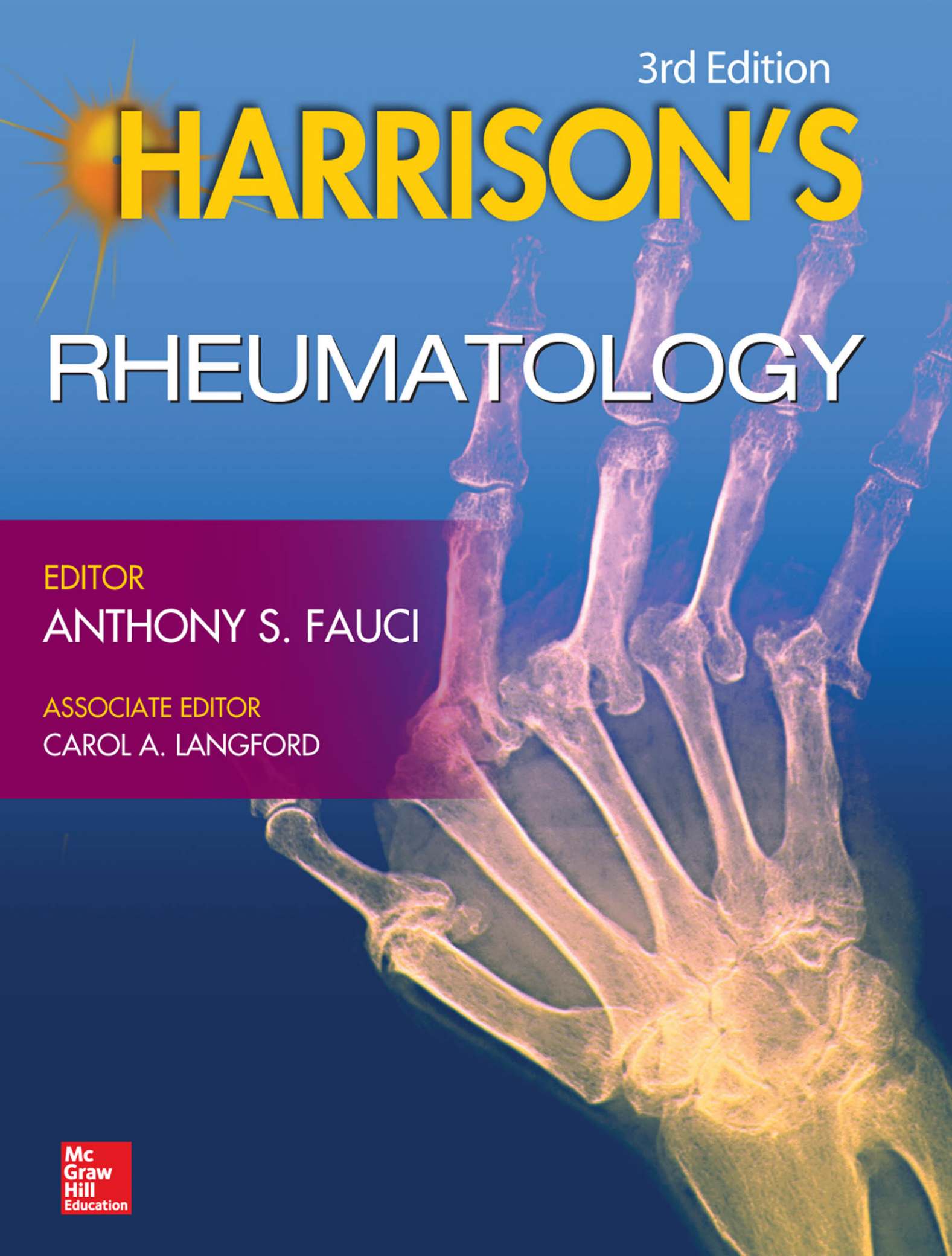
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HARRISON'S

RHEUMATOLOGY

EDITOR
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3rd Edition

HARRISON'S™ RHEUMATOLOGY

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PREFACE

Welcome to the third edition of *Harrison's Rheumatology*. This sectional volume, which is comprised of the rheumatology and immunology chapters contained in the 18th edition of *Harrison's Principles of Internal Medicine*, was originally introduced with the goal of providing knowledge to enhance the care of patients with rheumatic diseases and in recognition of the importance of rheumatology to the practice of internal medicine. With the changes and growth that have occurred both in the field of rheumatology and among populations across the world, particularly the increased number of aging people, the significance of these original foundations to patient care have become even greater over time.

While rheumatic diseases can affect people of all ages, many forms of arthritis and connective tissue disorders increase in frequency with age. This includes diverse disease processes such as osteoarthritis, rheumatoid arthritis, Sjögren's syndrome, crystalline arthropathies, polymyalgia rheumatica, and giant cell arteritis. The global population is continuing to grow with current analyses demonstrating over 300 million people currently living in the United States with 7 billion people world-wide. Life-expectancy also continues to rise and by 2030, it is estimated that almost 20% of the United States population will be 65 years and older. While the advancements in medicine will allow many older individuals to lead longer healthier lives, this means that there will also be an increasing proportion of the world's population who will develop and require care for rheumatic diseases.

In facing this challenge, we are aided by an accelerating understanding of the pathophysiology and treatment of rheumatic diseases. The strong relationship that exists between rheumatology and immunology has long stimulated biomedical investigation into the mechanisms involved in disease pathogenesis. In a short span of time, hypotheses about the role of the immune system in rheumatic diseases that were initially based on histologic evidence of tissue inflammation were able to be studied with ever increasing detail and precision. The findings from this research, together with the ability to impact specific immune effector functions have changed the management of many rheumatic diseases. With each edition of *Harrison's Rheumatology* we have seen the introduction of novel insights that have reduced pain, lessened joint and organ damage, and improved overall patient outcome, which provides us with great anticipation for what new advances the future of rheumatology will bring.

With the expansion of both patient numbers and scientific information, there also comes an increased need for practitioners who are knowledgeable about rheumatology. While the primary purpose of *Harrison's Rheumatology* is to provide the most updated information about the rheumatic diseases, we also hope that it will inspire clinical and scientific interest in this dynamic field. In so many ways, rheumatology embodies the essence of internal medicine through its diagnostic challenges, multisystem diseases, and complex therapeutics. With the potential that now exists in rheumatology to improve quality of life and daily functioning as well as to turn life-threatening diseases into chronic illnesses, practitioners can make profound short- and long-term differences in the lives of their patients. The example that rheumatology brings in being able to combine the opportunity for continuous intellectual growth with the privilege of providing skilled, compassionate, and meaningful care to patients reminds us regularly of the reasons why we chose to pursue a life in medicine.

The publication of this sectional would not be possible without the contributions of our skilled authors. It is also important to recognize the many dedicated individuals who conduct the basic, translational, and clinical investigations in rheumatology and immunology that are described in these pages and that have advanced this field. It is the continued hope of the Editors that *Harrison's Rheumatology* enhances your ability to care for patients with rheumatic diseases and heightens your appreciation of this challenging and fulfilling specialty.

Anthony S. Fauci, MD
Carol A. Langford, MD, MHS

NOTICE

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Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Hemnes AR (eds). *Harrison's Self-Assessment and Board Review*, 18th ed. New York, McGraw-Hill, 2012, ISBN 978-0-07-177195-5.



The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.



The genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

CHAPTER 1

INTRODUCTION TO THE IMMUNE SYSTEM

Barton F. Haynes ■ Kelly A. Soderberg ■ Anthony S. Fauci

DEFINITIONS

- *Adaptive immune system*—recently evolved system of immune responses mediated by T and B lymphocytes. Immune responses by these cells are based on specific antigen recognition by clonotypic receptors that are products of genes that rearrange during development and throughout the life of the organism. Additional cells of the adaptive immune system include various types of antigen-presenting cells.
- *Antibody*—B cell–produced molecules encoded by genes that rearrange during B cell development consisting of immunoglobulin heavy and light chains that together form the central component of the B cell receptor for antigen. Antibody can exist as B cell–surface antigen-recognition molecules or as secreted molecules in plasma and other body fluids (Table 1-13).
- *Antigens*—foreign or self-molecules that are recognized by the adaptive and innate immune systems resulting in immune cell triggering, T cell activation, and/or B cell antibody production.
- *Antimicrobial peptides*—small peptides <100 amino acids in length that are produced by cells of the innate immune system and have anti-infectious agent activity (Table 1-2).
- *Apoptosis*—the process of *programmed cell death* whereby signaling through various "death receptors" on the surface of cells [e.g., tumor necrosis factor (TNF) receptors, CD95] leads to a signaling cascade that involves activation of the caspase family of molecules and leads to DNA cleavage and cell death. Apoptosis, which does not lead to induction of inordinate inflammation, is to be contrasted with *cell necrosis*, which does lead to induction of inflammatory responses.
- *Autoimmune diseases*—diseases such as systemic lupus erythematosus and rheumatoid arthritis in which cells of the adaptive immune system such as autoreactive T and B cells become overreactive and produce self-reactive T cell and antibody responses.
- *Autoinflammatory diseases*—hereditary disorders such as hereditary periodic fevers (HPFs) characterized by recurrent episodes of severe inflammation and fever due to mutations in controls of the innate inflammatory response, i.e., the inflammasome (discussed later and in Table 1-6). Patients with HPFs also have rashes and serosal and joint inflammation and some can have neurologic symptoms. Autoinflammatory diseases are different from autoimmune diseases in that evidence for activation of adaptive immune cells such as autoreactive B cells is not present.
- *B cell receptor for antigen*—complex of surface molecules that rearrange during postnatal B cell development, made up of surface immunoglobulin (Ig) and associated Ig αβ chain molecules that recognize nominal antigen via Ig heavy- and light-chain variable regions, and signal the B cell to terminally differentiate to make antigen-specific antibody (Fig. 1-8).
- *B lymphocytes*—bone marrow–derived or bursal-equivalent lymphocytes that express surface immunoglobulin (the B cell receptor for antigen) and secrete specific antibody after interaction with antigen (Figs. 1-2 and 1-6).
- *CD classification of human lymphocyte differentiation antigens*—the development of monoclonal antibody technology led to the discovery of a large number of new leukocyte surface molecules. In 1982, the First International Workshop on Leukocyte Differentiation Antigens was held to establish a nomenclature for cell-surface molecules of human leukocytes. From this and subsequent leukocyte differentiation workshops has come the *cluster of differentiation* (CD) classification of leukocyte antigens (Table 1-1).

- *Chemokines*—soluble molecules that direct and determine immune cell movement and circulation pathways.
- *Complement*—cascading series of plasma enzymes and effector proteins whose function is to lyse pathogens and/or target them to be phagocytized by neutrophils and monocyte/macrophage lineage cells of the reticuloendothelial system (Fig. 1-5).
- *Co-stimulatory molecules*—molecules of antigen-presenting cells (such as B7-1 and B7-2 or CD40) that lead to T cell activation when bound by ligands on activated T cells (such as CD28 or CD40 ligand) (Fig. 1-7).
- *Cytokines*—soluble proteins that interact with specific cellular receptors that are involved in the regulation of the growth and activation of immune cells and mediate normal and pathologic inflammatory and immune responses (Tables 1-7, 1-9, and 1-10).
- *Dendritic cells*—myeloid and/or lymphoid lineage antigen-presenting cells of the adaptive immune system. Immature dendritic cells, or dendritic cell precursors, are key components of the innate immune system by responding to infections with production of high levels of cytokines. Dendritic cells are key initiators both of innate immune responses via cytokine production and of adaptive immune responses via presentation of antigen to T lymphocytes (Figs. 1-2 and 1-3, Table 1-5).
- *Inflammasome*—large cytoplasmic complexes of intracellular proteins that link the sensing of microbial products and cellular stress to the proteolytic activation of interleukin (IL)-1β and IL-18 inflammatory cytokines. Activation of molecules in the inflammasome is a key step in the response of the innate immune system for intracellular recognition of microbial and other danger signals in both health and pathologic states (Table 1-6).
- *Innate immune system*—ancient immune recognition system of host cells bearing germ line–encoded pattern recognition receptors (PRRs) that recognize pathogens and trigger a variety of mechanisms of pathogen elimination. Cells of the innate immune system include natural killer cell lymphocytes, monocytes/macrophages, dendritic cells, neutrophils, basophils, eosinophils, tissue mast cells, and epithelial cells (Tables 1-2 to 1-5 and 1-12).
- *Large granular lymphocytes*—lymphocytes of the innate immune system with azurophilic cytotoxic granules that have natural killer cell activity capable of killing foreign and host cells with few or no self–major histocompatibility complex (MHC) class I molecules (Fig. 1-4).
- *Natural killer cells*—large granular lymphocytes that kill target cells expressing few or no human leukocyte antigen (HLA) class I molecules, such as malignantly transformed cells and virally infected cells. Natural killer cells express receptors that inhibit killer cell function when self–major histocompatibility complex class I is present (Fig. 1-4).
- *Natural killer (NK) T cells* —innate-like lymphocytes that use an invariant T cell receptor (TCR)-α chain combined with a limited set of TCR-β chains and coexpress receptors commonly found on NK cells. NK T cells recognize lipid antigens of bacterial, viral, fungal, and protozoal infectious agents.
- *Pathogen-associated molecular patterns* (PAMPs)—Invariant molecular structures expressed by large groups of microorganisms that are recognized by host cellular pattern recognition receptors in the mediation of innate immunity (Fig. 1-1).
- *Pattern recognition receptors* (PRRs)—germ line–encoded receptors expressed by cells of the innate immune system that recognize pathogen-associated molecular patterns (Table 1-3).
- *Polyreactive natural antibodies*—preexisting low-affinity antibodies produced by innate B cells that cross-react with multiple antigens and are available at the time of infection to bind to and coat the invading pathogen and harness innate responses to slow the infection until an adaptive high-affinity protective antibody response can be made.
- *T cell receptor (TCR) for antigen*—complex of surface molecules that rearrange during postnatal T cell development made up of clonotypic TCR-α and -β chains that are associated with the CD3 complex composed of invariant γ, δ, ε, ζ, and η chains. TCR-α and -β chains recognize peptide fragments of protein antigen physically bound in antigen-presenting cell major histocompatibility complex class I or II molecules, leading to signaling via the CD3 complex to mediate effector functions (Fig. 1-7).
- *T cells*—thymus-derived lymphocytes that mediate adaptive cellular immune responses including T helper, T regulatory, and cytotoxic T lymphocyte effector cell functions (Figs. 1-2, 1-3, and 1-7).
- *Tolerance*—B and T cell nonresponsiveness to antigens that results from encounter with foreign or self-antigens by B and T lymphocytes in the absence of expression of antigen-presenting cell co-stimulatory molecules. Tolerance to antigens may be induced and maintained by multiple mechanisms either centrally (in the thymus for T cells or bone marrow for B cells) or peripherally at sites throughout the peripheral immune system.

INTRODUCTION

The human immune system has evolved over millions of years from both invertebrate and vertebrate organisms to develop sophisticated defense mechanisms to protect the host from microbes and their virulence factors.

The normal immune system has three key properties: a highly diverse repertoire of antigen receptors that enables recognition of a nearly infinite range of pathogens; immune memory, to mount rapid recall immune responses; and immunologic tolerance, to avoid immune damage to normal self-tissues. From invertebrates, humans have inherited the *innate immune system*, an ancient defense system that uses germ line–encoded proteins to recognize pathogens. Cells of the innate immune system, such as macrophages, dendritic cells, and natural killer (NK) lymphocytes, recognize pathogen-associated molecular patterns (PAMPs) that are highly conserved among many microbes and use a diverse set of pattern recognition receptor molecules (PRRs). Important components of the recognition of microbes by the innate immune system include (1) recognition by germ line–encoded host molecules, (2) recognition of key microbe virulence factors but not recognition of self-molecules, and (3) nonrecognition of benign foreign molecules or microbes. Upon contact with pathogens, macrophages and NK cells may kill pathogens directly or, in concert with dendritic cells, may activate a series of events that both slow the infection and recruit the more recently evolved arm of the human immune system, the *adaptive immune system*.

Adaptive immunity is found only in vertebrates and is based on the generation of antigen receptors on T and B lymphocytes by gene rearrangements, such that individual T or B cells express unique antigen receptors on their surface capable of specifically recognizing diverse antigens of the myriad infectious agents in the environment. Coupled with finely tuned specific recognition mechanisms that maintain tolerance (nonreactivity) to self-antigens, T and B lymphocytes bring both *specificity* and *immune memory* to vertebrate host defenses.

This chapter describes the cellular components, key molecules **(Table 1-1)**, and mechanisms that make up the innate and adaptive immune systems and describes how adaptive immunity is recruited to the defense of the host by innate immune responses. An appreciation of the cellular and molecular bases of innate and adaptive immune responses is critical to understanding the pathogenesis of inflammatory, autoimmune, infectious, and immunodeficiency diseases.

THE INNATE IMMUNE SYSTEM

All multicellular organisms, including humans, have developed the use of a limited number of surface and intracellular germ line–encoded molecules that recognize large groups of pathogens. Because of the myriad human pathogens, host molecules of the human innate immune system sense "danger signals" and either recognize PAMPs, the common molecular structures shared by many pathogens, or recognize host cell molecules produced in response to infection such as heat shock proteins and fragments of the extracellular matrix. PAMPs must be conserved structures vital to pathogen virulence and survival, such as bacterial endotoxin, so that pathogens cannot mutate molecules of PAMPs to evade human innate immune responses. PRRs are host proteins of the innate immune system that recognize PAMPs as host danger signal molecules **(Tables 1-2** and **1-3)**. Thus, recognition of pathogen molecules by hematopoietic and nonhematopoietic cell types leads to activation/production of the complement cascade, cytokines, and antimicrobial peptides as effector molecules. In addition, pathogen PAMPs as host danger signal molecules activate dendritic cells to mature and to express molecules on the dendritic cell surface that optimize antigen presentation to respond to foreign antigens.

PATTERN RECOGNITION

Major PRR families of proteins include C-type lectins, leucine-rich proteins, macrophage scavenger receptor proteins, plasma pentraxins, lipid transferases, and integrins (Table 1-3). A major group of PRR collagenous glycoproteins with C-type lectin domains are termed *collectins* and include the serum protein mannose-binding lectin (MBL). MBL and other collectins, as well as two other protein families—the pentraxins (such as C-reactive protein and serum amyloid P) and macrophage scavenger receptors—all have the property of opsonizing (coating) bacteria for phagocytosis by macrophages and can also activate the complement cascade to lyse bacteria. Integrins are cell-surface adhesion molecules that signal after cells bind bacterial lipopolysaccharide (LPS) and activate phagocytic cells to ingest pathogens.

There are multiple connections between the innate and adaptive immune systems; these include (1) a plasma protein, LPS-binding protein, which binds and transfers LPS to the macrophage LPS receptor, CD14; (2) a human family of proteins called *Toll-like receptor proteins* (TLRs), some of which are associated with CD14, bind LPS, and signal epithelial cells, dendritic cells, and macrophages to produce cytokines and upregulate cell-surface molecules that signal the initiation of adaptive immune responses **(Fig. 1-1**, Tables 1-3 and **1-4)**, and (3) families of intracellular microbial sensors called NOD-like receptors (NLRs) and RIG-like helicases (RLHs). Proteins in the Toll family can be expressed on macrophages, dendritic cells, and B cells as well as on a variety of nonhematopoietic cell types, including respiratory epithelial cells. Ten TLRs have been identified in humans and 13 TLRs in mice (Tables 1-4 and **1-5**). Upon ligation, TLRs activate a series of intracellular events that lead to the killing

TABLE 1-1

HUMAN LEUKOCYTE SURFACE ANTIGENS—THE CD CLASSIFICATION OF LEUKOCYTE DIFFERENTIATION ANTIGENS

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, kDa	DISTRIBUTION	LIGAND(S)	FUNCTION
CD1a (T6, HTA-1)	Ig	49	CD, cortical thymocytes, Langerhans type of dendritic cells	TCRγδ T cells	CD1 molecules present lipid antigens of intracellular bacteria such as *Mycobacterium leprae* and *M. tuberculosis* to TCRγδ T cells.
CD1b	Ig	45	CD, cortical thymocytes, Langerhans type of dendritic cells	TCRγδ T cells	
CD1c	Ig	43	DC, cortical thymocytes, subset of B cells, Langerhans type of dendritic cells	TCRγδ T cells	
CD1d	Ig	?	Cortical thymocytes, intestinal epithelium, Langerhans type of dendritic cells	TCRγδ T cells	
CD2 (T12, LFA-2)	Ig	50	T, NK	CD58, CD48, CD59, CD15	Alternative T cell activation, T cell anergy, T cell cytokine production, T- or NK-mediated cytolysis, T cell apoptosis, cell adhesion
CD3 (T3, Leu-4)	Ig	γ:25–28, δ:21–28, ε:20–25, η:21–22, ζ:16	T	Associates with the TCR	T cell activation and function; ζ is the signal transduction component of the CD3 complex
CD4 (T4, Leu-3)	Ig	55	T, myeloid	MHC-II, HIV, gp120, IL-16, SABP	T cell selection, T cell activation, signal transduction with p56*lck*, primary receptor for HIV
CD7 (3A1, Leu-9)	Ig	40	T, NK	K-12 (CD7L)	T and NK cell signal transduction and regulation of IFN-γ, TNF-α production
CD8 (T8, Leu-2)	Ig	34	T	MHC-I	T cell selection, T cell activation, signal transduction with p56*lck*
CD14 (LPS-receptor)	LRG	53–55	M, G (weak), not by myeloid progenitors	Endotoxin (lipopolysaccharide), lipoteichoic acid, PI	TLR4 mediates with LPS and other PAMP activation of innate immunity
CD19 B4	Ig	95	B (except plasma cells), FDC	Not known	Associates with CD21 and CD81 to form a complex involved in signal transduction in B cell development, activation, and differentiation
CD20 (B1)	Unassigned	33–37	B (except plasma cells)	Not known	Cell signaling, may be important for B cell activation and proliferation
CD21 (B2, CR2, EBV-R, C3dR)	RCA	145	Mature B, FDC, subset of thymocytes	C3d, C3dg, iC3b, CD23, EBV	Associates with CD19 and CD81 to form a complex involved in signal transduction in B cell development, activation, and differentiation; Epstein-Barr virus receptor

(*continued*)

TABLE 1-1

HUMAN LEUKOCYTE SURFACE ANTIGENS—THE CD CLASSIFICATION OF LEUKOCYTE DIFFERENTIATION ANTIGENS (*CONTINUED*)

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, KDA	DISTRIBUTION	LIGAND(S)	FUNCTION
CD22 (BL-CAM)	Ig	130–140	Mature B	CDw75	Cell adhesion, signaling through association with p72*sky*, p53/56*lyn*, PI3 kinase, SHP1, fLCγ
CD23 (FcεRII, B6, Leu-20, BLAST-2)	C-type lectin	45	B, M, FDC	IgE, CD21, CD11b, CD11c	Regulates IgE synthesis, cytokine release by monocytes
CD28	Ig	44	T, plasma cells	CD80, CD86	Co-stimulatory for T cell activation; involved in the decision between T cell activation and anergy
CD40	TNFR	48–50	B, DC, EC, thymic epithelium, MP, cancers	CD154	B cell activation, proliferation, and differentiation; formation of GCs; isotype switching; rescue from apoptosis
CD45 (LCA, T200, B220)	PTP	180, 200, 210, 220	All leukocytes	Galectin-1, CD2, CD3, CD4	T and B activation, thymocyte development, signal transduction, apoptosis
CD45RA	PTP	210, 220	Subset T, medullary thymocytes, "naive" T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 4 (A), restricted to a subset of T cells
CD45RB	PTP	200, 210, 220	All leukocytes	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 5 (B)
CD45RC	PTP	210, 220	Subset T, medullary thymocytes, "naive" T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 6 (C), restricted to a subset of T cells
CD45RO	PTP	180	Subset T, cortical thymocytes, "memory" T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing no differentially spliced exons, restricted to a subset of T cells
CD80 (B7-1, BB1)	Ig	60	Activated B and T, MP, DC	CD28, CD152	Co-regulator of T cell activation; signaling through CD28 stimulates and through CD152 inhibits T cell activation
CD86 (B7-2, B70)	Ig	80	Subset B, DC, EC, activated T, thymic epithelium	CD28, CD152	Co-regulator of T cell activation; signaling through CD28 stimulates and through CD152 inhibits T cell activation
CD95 (APO-1, Fas)	TNFR	135	Activated T and B	Fas ligand	Mediates apoptosis
CD152 (CTLA-4)	Ig	30–33	Activated T	CD80, CD86	Inhibits T cell proliferation
CD154 (CD40L)	TNF	33	Activated CD4+ T, subset CD8+ T, NK, M, basophil	CD40	Co-stimulatory for T cell activation, B cell proliferation and differentiation

Abbreviations: CTLA, cytotoxic T lymphocyte–associated protein; DC, dendritic cells; EBV, Epstein-Barr virus; EC, endothelial cells; ECM, extracellular matrix; Fcγ RIIIA, low-affinity IgG receptor isoform A; FDC, follicular dendritic cells; G, granulocytes; GC, germinal center; GPI, glycosyl phosphatidylinositol; HTA, human thymocyte antigen; IgG, immunoglobulin G; LCA, leukocyte common antigen; LPS, lipopolysaccharide; MHC-I, major histocompatibility complex class I; MP, macrophages; Mr, relative molecular mass; NK, natural killer cells; P, platelets; PBT, peripheral blood T cells; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PTP, protein tyrosine phosphatase; TCR, T cell receptor; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor. For an expanded list of cluster of differentiation (CD) human antigens, see Harrison's Online at *http://www.accessmedicine.com;* and for a full list of CD human antigens from the most recent Human Workshop on Leukocyte Differentiation Antigens (VII), see *http://mpr.nci.nih.gov/prow/*.

Source: Compiled from T Kishimoto et al (eds): *Leukocyte Typing VI*, New York, Garland Publishing 1997; R Brines et al: Immunology Today 18S:1, 1997; and S Shaw (ed): *Protein Reviews on the Web, http://mpr.nci.nih.gov/prow/*.

TABLE 1-2

MAJOR COMPONENTS OF THE INNATE IMMUNE SYSTEM	
Pattern recognition receptors (PRR)	C-type lectins, leucine-rich proteins, scavenger receptors, pentraxins, lipid transferases, integrins, inflammasome proteins
Antimicrobial peptides	α-Defensins, β-defensins, cathelin, protegrin, granulysin, histatin, secretory leukoprotease inhibitor, and probiotics
Cells	Macrophages, dendritic cells, NK cells, NK-T cells, neutrophils, eosinophils, mast cells, basophils, and epithelial cells
Complement components	Classic and alternative complement pathway, and proteins that bind complement components
Cytokines	Autocrine, paracrine, endocrine cytokines that mediate host defense and inflammation, as well as recruit, direct, and regulate adaptive immune responses

Abbreviation: NK cells, natural killer cells.

of bacteria- and viral-infected cells as well as to the recruitment and ultimate activation of antigen-specific T and B lymphocytes (Fig. 1-1). Importantly, signaling by massive amounts of LPS through TLR4 leads to the release of large amounts of cytokines that mediate LPS-induced shock. Mutations in TLR4 proteins in mice protect from LPS shock, and TLR mutations in humans protect from LPS-induced inflammatory diseases such as LPS-induced asthma (Fig. 1-1).

Two other families of intracellular PRRs are the NLRs (NOD-like receptors) and the RLHs (RIG-like helicases). These families, unlike the TLRs, are composed primarily of soluble intracellular proteins that scan the cytoplasm for intracellular pathogens (Tables 1-2 and 1-3).

The intracellular microbial sensors, NLRs, after triggering, form large cytoplasmic complexes termed *inflammasomes*, which are aggregates of molecules including NOD-like receptor pyrin (NLRP) proteins that are members of the NLR family (Table 1-3). Inflammasomes activate inflammatory caspases and IL-1β in the

TABLE 1-3

MAJOR PATTERN RECOGNITION RECEPTORS (PRR) OF THE INNATE IMMUNE SYSTEM

PRR PROTEIN FAMILY	SITES OF EXPRESSION	EXAMPLES	LIGANDS (PAMPS)	FUNCTIONS OF PRR
Toll-like receptors	Multiple cell types	TLR2-10	Bacterial and viral carbohydrates	Activate innate immune cells to respond to multiple pathogens and initiate adaptive immune responses
C-type lectins	Plasma proteins	Collectins		Opsonization of bacteria and virus, activation of complement
Humoral			Terminal mannose	
Cellular	Macrophages, dendritic cell	Macrophage mannose receptor	Carbohydrate on HLA molecules	Phagocytosis of pathogens
	Natural killer (NK) cells	NKG2-A		Inhibits killing of host cells expressing HLA + self-peptides
Leucine-rich proteins	Macrophages, dendritic cells, epithelial cells	CD14	Lipopolysaccharide (LPS)	Binds LPS and Toll proteins
Scavenger receptors	Macrophage	Macrophage scavenger receptors	Bacterial cell walls	Phagocytosis of bacteria
Pentraxins	Plasma protein	C-reactive proteins	Phosphatidyl choline	Opsonization of bacteria, activation of complement
	Plasma protein	Serum amyloid P	Bacterial cell walls	Opsonization of bacteria, activation of complement
Lipid transferases	Plasma protein	LPS binding protein	LPS	Binds LPS, transfers LPS to CD14
Integrins	Macrophages, dendritic cells, NK cells	CD11b,c; CD18	LPS	Signals cells, activates phagocytosis
NOD-like receptors	Innate cells	NALP-3	Viral DNA bacterial muramyl dipeptide	Cytosolic proteins involved in innate sensing

Abbreviation: PAMPs, pathogen-associated molecular patterns.
Source: Adapted from R Medzhitov, CA Janeway: Curr Opin Immunol 9:4, 1997. Copyright 1997, with permission from Elsevier.

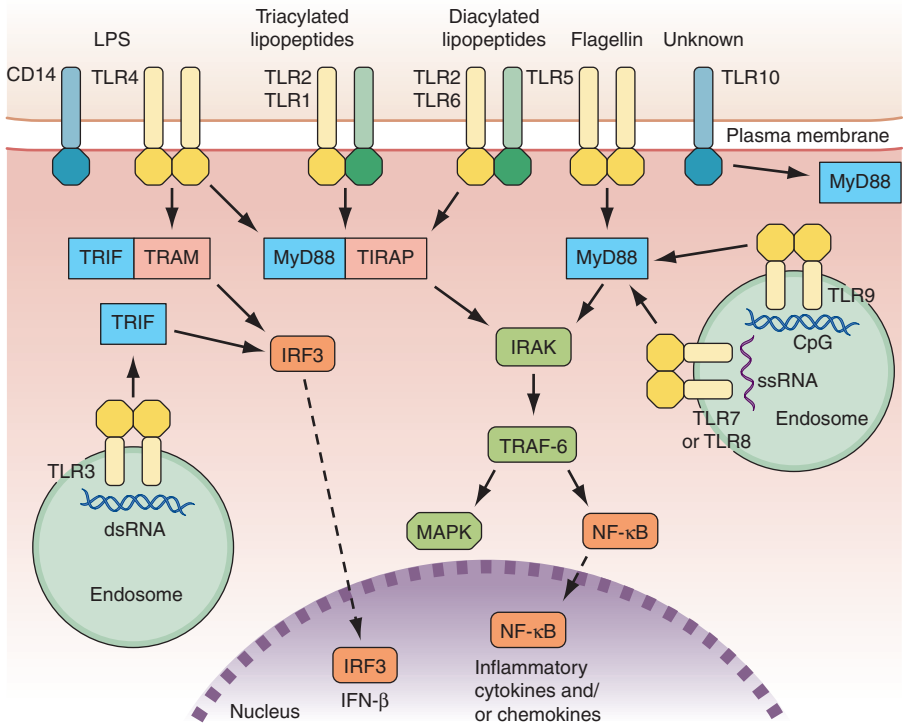


FIGURE 1-1

Overview of major TLR signaling pathways. All TLRs signal through MyD88, with the exception of TLR3. TLR4 and the TLR2 subfamily (TLR1, TLR2, TLR6) also engage TIRAP. TLR3 signals through TRIF. TRIF is also used in conjunction with TRAM in the TLR4–MyD88-independent pathway. Dashed arrrows indicate translocation into the nucleus. LPS, lipopolysaccharide; dsRNA, double-strand RNA; ssRNA, single-strand RNA; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; IFN, interferon; IRF3, interferon regulatory factor 3; TLR, Toll-like receptor. (*Adapted from D van Duin et al: Trends Immunol 27:49, 2006; with permission.*)

presence of nonbacterial danger signals (cell stress) and bacterial PAMPs. Mutations in inflammasome proteins can lead to chronic inflammation in a group of periodic febrile diseases called *autoinflammatory syndromes* **(Table 1-6)**.

EFFECTOR CELLS OF INNATE IMMUNITY

Cells of the innate immune system and their roles in the first line of host defense are listed in Table 1-5. Equally important as their roles in the mediation of innate immune responses are the roles that each cell type plays in recruiting T and B lymphocytes of the adaptive immune system to engage in specific antipathogen responses.

Monocytes-macrophages

Monocytes arise from precursor cells within bone marrow **(Fig. 1-2)** and circulate with a half-life ranging from 1 to 3 days. Monocytes leave the peripheral circulation by marginating in capillaries and migrating into a vast extravascular pool. Tissue macrophages arise from monocytes that have migrated out of the circulation and by in situ proliferation of macrophage precursors in tissue. Common locations where tissue macrophages (and certain of their specialized forms) are found are lymph node, spleen, bone marrow, perivascular connective tissue, serous cavities such as the peritoneum, pleura, skin connective tissue, lung (alveolar macrophages), liver (Kupffer cells), bone (osteoclasts), central nervous system (microglia cells), and synovium (type A lining cells).

In general, monocytes-macrophages are on the first line of defense associated with innate immunity and ingest and destroy microorganisms through the release of toxic products such as hydrogen peroxide (H_2O_2) and nitric oxide (NO). Inflammatory mediators produced by macrophages attract additional effector cells such as neutrophils to the site of infection. Macrophage mediators include prostaglandins; leukotrienes; platelet activating factor; cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-6, and IL-12; and chemokines **(Tables 1-7** to **1-10)**.

Although monocytes-macrophages were originally thought to be the major antigen-presenting cells (APCs) of the immune system, it is now clear that cell types called dendritic cells are the most potent and effective APCs in the body (discussed later). Monocytes-macrophages

TABLE 1-4

THE ROLE OF PATTERN RECOGNITION RECEPTORS (PRRS) IN MODULATION OF ADAPTIVE IMMUNE RESPONSES

PRR FAMILY	PRRS	LIGAND	DC OR MACROPHAGE CYTOKINE RESPONSE	ADAPTIVE IMMUNE RESPONSE
TLRs	TLR2 (heterodimer with TLR1 or 6)	Lipopeptides Pam-3-cys (TLR 2/1) MALP (TLR 2/6)	Low IL-12p70 High IL-10 IL-6	T_H1 T_H2 T regulatory
	TLR3	dsRNA	IL-12p70 IFN-α IL-6	T_H1
	TLR4	*E. coli* LPS	High IL-12p70 Intermediate IL-10 IL-6	T_H1
	TLR5	Flagellin	High IL-12p70 Low IL-12p70	T_H1 T_H2
	TLR7/8	ssRNA Imidazoquinolines	High IL-12p70 IFN-α IL-6	T_H1
	TLR9	CpG DNA	High IL-12p70 Low IL-10 IL-6 IFN-α	T_H1
	TLR10	?	?	?
C-type lectins	DC-SIGN	Env of HIV; core protein of HCV; components of *Mycobacterium tuberculosis; Helicobacter pylori,* Lewis Ag	*H. pylori*, Lewis Ag Suppresses IL-12p70 Suppresses TLR signaling in DCs	T_H2 T regulatory
NOD	NOD2	Muramyl dipeptide of peptidoglycan	Induces IL-10 in DCs	Weak T cell response (tolerogenic?)
Mannose receptor	Mannose receptor	Mannosylated lipoarabinomannans from bacillus Calmette-Guerin and *M. tuberculosis*	Suppresses IL-12 and TLR signaling in DCs	Weak T cell response? (tolerogenic?)

Abbreviations: dsRNA, double-strand RNA; ssRNA, single-strand RNA; LPS, lipopolysaccharide; T_H2, helper T cell; T_H1, helper T cell; CpG, sequences in DNA recognized by TLR-9; MALP, macrophage-activating lipopeptide; DC-SIGN, DC-specific C-type lectin; NOD, NOTCH protein domain; TLR, Toll-like receptor; HCV, hepatitis C.

Source: B Pulendran: J Immunol 174:2457, 2005. Copyright 2005 The American Association of Immunologists, Inc., with permission.

mediate innate immune effector functions such as destruction of antibody-coated bacteria, tumor cells, or even normal hematopoietic cells in certain types of autoimmune cytopenias. Monocytes-macrophages ingest bacteria or are infected by viruses, and in doing so, they frequently undergo programmed cell death or *apoptosis*. Macrophages that are infected by intracellular infectious agents are recognized by dendritic cells as infected and apoptotic cells and are phagocytosed by dendritic cells. In this manner, dendritic cells "cross-present" infectious agent antigens of macrophages to T cells. Activated macrophages can also mediate antigen-nonspecific lytic activity and eliminate cell types such as tumor cells in the absence of antibody. This activity is largely mediated by cytokines (i.e., TNF-α and IL-1). Monocytes-macrophages express lineage-specific molecules (e.g., the cell-surface LPS receptor, CD14) as well as surface receptors for a number of molecules, including the Fc region of IgG, activated complement components, and various cytokines (Table 1-7).

Dendritic cells

Human dendritic cells (DCs) are heterogenous and contain several subsets, including myeloid DCs and plasmacytoid DCs. Myeloid DCs can differentiate into either macrophages-monocytes or tissue-specific DCs. In contrast to myeloid DCs, plasmacytoid DCs are inefficient antigen-presenting cells but are potent producers of type I interferon (IFN) (e.g., IFN-α) in response to

TABLE 1-5

CELLS OF THE INNATE IMMUNE SYSTEM AND THEIR MAJOR ROLES IN TRIGGERING ADAPTIVE IMMUNITY

CELL TYPE	MAJOR ROLE IN INNATE IMMUNITY	MAJOR ROLE IN ADAPTIVE IMMUNITY
Macrophages	Phagocytose and kill bacteria; produce antimicrobial peptides; bind (LPS); produce inflammatory cytokines	Produce IL-1 and TNF-α to upregulate lymphocyte adhesion molecules and chemokines to attract antigen-specific lymphocyte. Produce IL-12 to recruit T_H1 T helper cell responses; upregulate co-stimulatory and MHC molecules to facilitate T and B lymphocyte recognition and activation. Macrophages and dendritic cells, after LPS signaling, upregulate co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) that are required for activation of antigen-specific antipathogen T cells. There are also Toll-like proteins on B cells and dendritic cells that, after LPS ligation, induce CD80 and CD86 on these cells for T cell antigen presentation.
Plasmacytoid f dendritic cells (DCs) of lymphoid lineage	Produce large amounts of interferon-α (IFN-α), which has antitumor and antiviral activity, and are found in T cell zones of lymphoid organs; they circulate in blood	IFN-α is a potent activator of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells
Myeloid dendritic cells are of two types; interstitial and Langerhans-derived	Interstitial DCs are strong producers of IL-12 and IL-10 and are located in T cell zones of lymphoid organs, circulate in blood, and are present in the interstices of the lung, heart, and kidney; Langerhans DCs are strong producers of IL-12; are located in T cell zones of lymph nodes, skin epithelia, and the thymic medulla; and circulate in blood	Interstitial DCs are potent activators of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells
Natural killer (NK) cells	Kill foreign and host cells that have low levels of MHC+ self-peptides. Express NK receptors that inhibit NK function in the presence of high expression of self-MHC.	Produce TNF-α and IFN-γ, which recruit T_H1 helper T cell responses
NK-T cells	Lymphocytes with both T cell and NK surface markers that recognize lipid antigens of intracellular bacteria such as *Mycobacterium tuberculosis* by CD1 molecules and kill host cells infected with intracellular bacteria.	Produce IL-4 to recruit T_H2 helper T cell responses, IgG1 and IgE production
Neutrophils	Phagocytose and kill bacteria, produce antimicrobial peptides	Produce nitric oxide synthase and nitric oxide, which inhibit apoptosis in lymphocytes and can prolong adaptive immune responses
Eosinophils	Kill invading parasites	Produce IL-5, which recruits Ig-specific antibody responses
Mast cells and basophils	Release TNF-α, IL-6, and IFN-γ in response to a variety of bacterial PAMPs	Produce IL-4, which recruits T_H2 helper T cell responses and recruit IgG1- and IgE-specific antibody responses
Epithelial cells	Produce antimicrobial peptides; tissue-specific epithelia produce mediator of local innate immunity; e.g., lung epithelial cells produce surfactant proteins (proteins within the collectin family) that bind and promote clearance of lung-invading microbes	Produces TGF-β, which triggers IgA-specific antibody responses

Abbreviations: LPS, lipopolysaccharide; PAMP, pathogen-associated molecular patterns; TNF-α, tumor necrosis factor-alpha; IL-4, IL-5, IL-6, IL-10, and IL-12, interleukin 4, 5, 6, 10, and 12, respectively.

Source: Adapted from R Medzhitov, CA Janeway: Curr Opinion Immunol 9:4, 1997. Copyright 1997, with permission from Elsevier.

TABLE 1-6

DISEASES ASSOCIATED WITH INFLAMMASOME ACTIVITY

DISEASE	CLINICAL FEATURES	GENE MUTATED	ETIOLOGIC AGENT	INFLAMMASOME INVOLVEMENT	*ANAKINRA RESPONSE
Familial cold autoinflammatory syndrome (FCAS)	Fever, arthralgia, cold-induced urticaria	NALP3		Overactive	Yes
Muckle-Wells syndrome (MWS)	Fever, arthralgia, urticaria, sensorineural deafness, amyloidosis	NAPL3		Overactive	Yes
Chronic infantile neurologic cutaneous and articular syndrome (CINCA, NOMID)	Fever, severe arthralgia, urticaria, neurologic problems, severe amyloidosis	NALP3		Overactive	Yes
Familial Mediterranean fever (FMF)	Fever, peritonitis, pleuritis, amyloidosis	Pyrin		Overactive	Partial
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)	Pyogenic sterile arthritis	PSTPIP1		Overactive	Yes
Hyperimmunoglobulin D syndrome (HIDS)	Arthralgia, abdominal pain, lymphadenopathy	Mevalonate kinase		To be demonstrated	Yes
Tumor necrosis factor receptor-1–associated syndrome (TRAPS)	Fever, abdominal pain, skin lesions	TNF-R1		To be demonstrated	Yes
Systemic onset juvenile idiopathic arthritis (SOJIA)	Chronic joint inflammation		Unknown	To be demonstrated	Yes
Adult-onset Still's disease (AOSD)	Arthralgia, fever		Unknown	To be demonstrated	Yes
Behçet's disease	Arthralgia, uveitis, ulcers		Unknown	To be demonstrated	Yes
Schnitzler's syndrome	Urticaria, fever, arthralgia		Unknown	To be demonstrated	Yes
Gout	Metabolic arthritis, pain		Uric acid (MSU)	Activated	Yes
Pseudogout	Arthritis		CPPD	Activated	Yes
Contact dermatitis	Urticaria		Irritants	Activated	Unknown
Fever syndrome	Fever	NALP12		Unknown	Unknown
Hydatidiform mole	Hydatid mole	NALP7		Unknown	Unknown
Vitiligo	Skin depigmentation, autoimmunity	NALP1		Unknown	Unknown

*Anakinra is a recombinant IL-1 receptor antagonist that functions to block the biologic activity of naturally occuring interleukin-1 (IL-1).
Source: From F Martinon et al: Ann Rev Immunol 27:229, 2009. Copyright 2009. Reproduced with permission from Annual Reviews Inc.

viral infections. The maturation of DCs is regulated through cell-to-cell contact and soluble factors, and DCs attract immune effectors through secretion of chemokines. When DCs come in contact with bacterial products, viral proteins, or host proteins released as danger signals from distressed host cells (Figs. 1-2 and 1-3), infectious agent molecules bind to various TLRs and activate DCs to release cytokines and chemokines that drive cells of the innate immune system to become activated to respond to the invading organism, and recruit T and B cells of the adaptive immune system to respond. Plasmacytoid DCs produce antiviral IFN-α that activates NK cell killing of pathogen-infected cells; IFN-α also activates T cells to mature into antipathogen cytotoxic (killer) T cells. Following contact with pathogens, both plasmacytoid and myeloid DCs produce chemokines

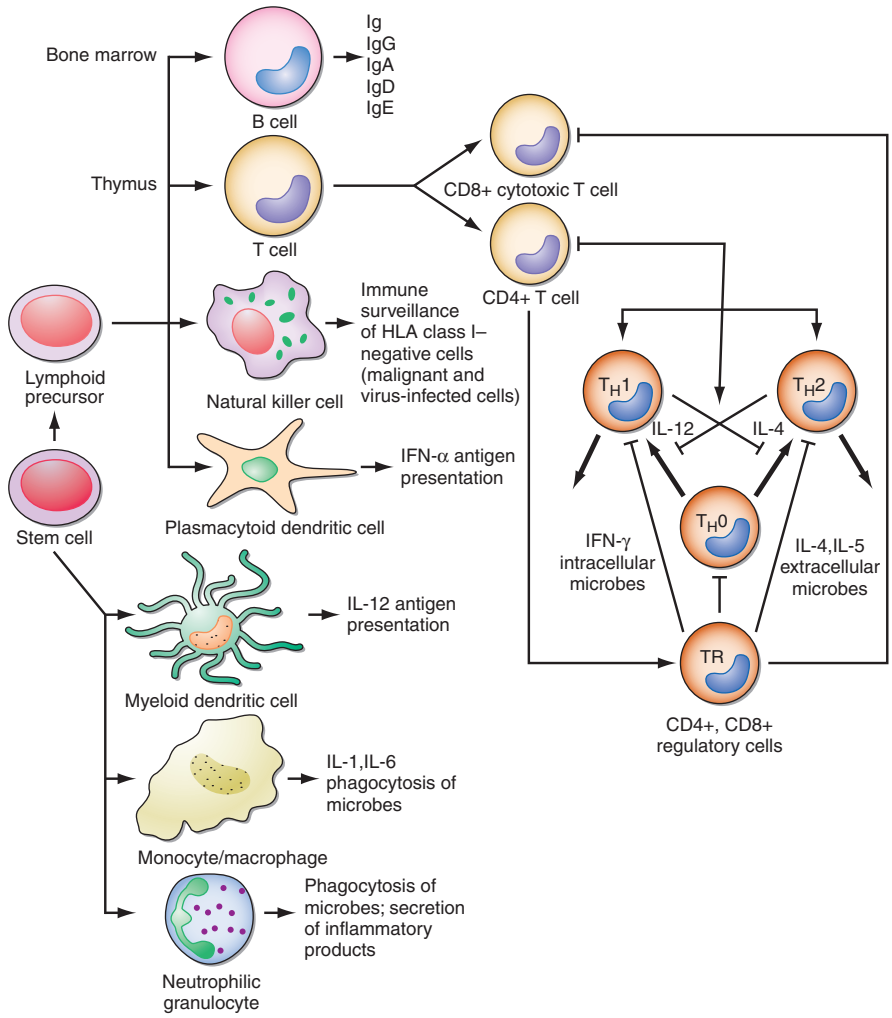


FIGURE 1-2

Schematic model of intercellular interactions of adaptive immune system cells. In this figure, the arrows denote that cells develop from precursor cells or produce cytokines or antibodies; lines ending with bars indicate suppressive intercellular interactions. Stem cells differentiate into either T cells, antigen-presenting dendritic cells, natural killer cells, macrophages, granulocytes, or B cells. Foreign antigen is processed by dendritic cells, and peptide fragments of foreign antigen are presented to CD4+ and/or CD8+ T cells. CD8+ T cell activation leads to induction of cytotoxic T lymphocyte (CTL) or killer T cell generation, as well as induction of cytokine-producing CD8+ cytotoxic T cells. For antibody production against the same antigen, active antigen is bound to sIg within the B cell receptor complex and drives B cell maturation into plasma cells that secrete Ig. T_H1 or T_H2 CD4+ T cells producing interleukin (IL) 4, IL-5, or interferon (IFN) γ regulate the Ig class switching and determine the type of antibody produced. T_H17 cells secrete IL-17, IL-22, IL-26, which contribute to host defense against extracellular bacteria and fungi, particularly at mucosal surfaces. CD4+, CD25+ T regulatory cells produce IL-10 and downregulate T and B cell responses once the microbe has been eliminated. GM-CSF, granulocyte-macrophage colony stimulating factor; TNF, tumor necrosis factor.

that attract helper and cytotoxic T cells, B cells, polymorphonuclear cells, and naïve and memory T cells as well as regulatory T cells to ultimately dampen the immune response once the pathogen is controlled. TLR engagement on DCs upregulates MHC class II, B7-1 (CD80), and B7-2 (CD86), which enhance DC-specific antigen presentation and induce cytokine production (Table 1-7). Thus, DCs are important bridges between early (innate) and later (adaptive) immunity. DCs also modulate and determine the types of immune responses induced by pathogens via the TLRs expressed on DCs (TLR7-9 on plasmacytoid DCs, TLR4 on monocytoid DCs) and via the TLR adapter proteins that are induced to associate with TLRs (Fig. 1-1, Table 1-4). In addition, other PRRs, such as C-type lectins, NLRs, and mannose receptors, upon ligation by pathogen products,

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
IL-1α,β	Type I IL-1r, Type II IL-1r	Monocytes/macrophages, B cells, fibroblasts, most epithelial cells including thymic epithelium, endothelial cells	All cells	Upregulates adhesion molecule expression, neutrophil and macrophage emigration, mimics shock, fever, upregulates hepatic acute-phase protein production, facilitates hematopoiesis
IL-2	IL-2r α,β, common γ	T cells	T cells, B cells, NK cells, monocytes-macrophages	Promotes T cell activation and proliferation, B cell growth, NK cell proliferation and activation, enhanced monocyte/macrophage cytolytic activity
IL-3	IL-3r, common β	T cells, NK cells, mast cells	Monocytes-macrophages, mast cells, eosinophils, bone marrow progenitors	Stimulates hematopoietic progenitors
IL-4	IL-4r α, common γ	T cells, mast cells, basophils	T cells, B cells, NK cells, monocytes-macrophages, neutrophils, eosinophils, endothelial cells, fibroblasts	Stimulates T_H2 helper T cell differentiation and proliferation. Stimulates B cell Ig class switch to IgG1 and IgE anti-inflammatory action on T cells, monocytes
IL-5	IL-5r α, common γ	T cells, mast cells, eosinophils	Eosinophils, basophils, murine B cells	Regulates eosinophil migration and activation
IL-6	IL-6r, gp130	Monocytes-macrophages, B cells, fibroblasts, most epithelium including thymic epithelium, endothelial cells	T cells, B cells, epithelial cells, hepatocytes, monocytes-macrophages	Induces acute-phase protein production, T and B cell differentiation and growth, myeloma cell growth, and osteoclast growth and activation
IL-7	IL-7r α, common γ	Bone marrow, thymic epithelial cells	T cells, B cells, bone marrow cells	Differentiates B, T, and NK cell precursors, activates T and NK cells
IL-8	CXCR1, CXCR2	Monocytes-macrophages, T cells, neutrophils, fibroblasts, endothelial cells, epithelial cells	Neutrophils, T cells, monocytes-macrophages, endothelial cells, basophils	Induces neutrophil, monocyte, and T cell migration, induces neutrophil adherence to endothelial cells and histamine release from basophils, and stimulates angiogenesis. Suppresses proliferation of hepatic precursors
IL-9	IL-9r α, common γ	T cells	Bone marrow progenitors, B cells, T cells, mast cells	Induces mast cell proliferation and function, synergizes with IL-4 in IgG and IgE production and T cell growth, activation, and differentiation
IL-10	IL-10r	Monocytes-macrophages, T cells, B cells, keratinocytes, mast cells	Monocytes-macrophages, T cells, B cells, NK cells, mast cells	Inhibits macrophage proinflammatory cytokine production, downregulates cytokine class II antigen and B7-1 and B7-2 expression, inhibits differentiation of T_H1 helper T cells, inhibits NK cell function, stimulates mast cell proliferation and function, B cell activation, and differentiation
IL-11	IL-11, gp130	Bone marrow stromal cells	Megakaryocytes, B cells, hepatocytes	Induces megakaryocyte colony formation and maturation, enhances antibody responses, stimulates acute-phase protein production

(*continued*)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (*CONTINUED*)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
IL-12 (35-kD and 40-kD subunits)	IL-12r	Activated macrophages, dendritic cells, neutrophils	T cells, NK cells	Induces T_H1 T helper cell formation and lymphokine-activated killer cell formation. Increases CD8+ CTL cytolytic activity; ↓IL-17, ↑IFN-γ.
IL-13	IL-13/IL-4	T cells (T_H2)	Monocytes-macrophages, B cells, endothelial cells, keratinocytes	Upregulates VCAM-1 and C-C chemokine expression on endothelial cells and B cell activation and differentiation, and inhibits macrophage proinflammatory cytokine production
IL-14	Unknown	T cells	Normal and malignant B cells	Induces B cell proliferation
IL-15	IL-15r α, common γ, IL2r β	Monocytes-macrophages, epithelial cells, fibroblasts	T cells, NK cells	Promotes T cell activation and proliferation, angiogenesis, and NK cells
IL-16	CD4	Mast cells, eosinophils, CD8+ T cells, respiratory epithelium	CD4+ T cells, monocytes-macrophages, eosinophils	Promotes chemoattraction of CD4+ T cells, monocytes, and eosinophils. Inhibits HIV replication. Inhibits T cell activation through CD3/T cell receptor
IL-17	IL17r	CD4+ T cells	Fibroblasts, endothelium, epithelium	Enhances cytokine secretion
IL-18	IL-18r (IL-1R-related protein)	Keratinocytes, macrophages	T cells, B cells, NK cells	Upregulates IFN-γ production, enhances NK cell cytotoxicity
IL-21	IL-δγ chain/ IL-21R	CD4 T cells	NK cells	Downregulates NK cell–activating molecules, NKG2D/DAP10
IL-23	IL-12Rb1/IL23R	Macrophages, other cell types	T cells	Opposite effects of IL-12 (↑IL-17, ↑IFN-γ)
IFN-α	Type I interferon receptor	All cells	All cells	Promotes antiviral activity. Stimulates T cell, macrophage, and NK cell activity. Direct antitumor effects. Upregulates MHC class I antigen expression. Used therapeutically in viral and autoimmune conditions
IFN-β	Type I interferon receptor	All cells	All cells	Antiviral activity. Stimulates T cell, macrophage, and NK cell activity. Direct antitumor effects. Upregulates MHC class I antigen expression. Used therapeutically in viral and autoimmune conditions
IFN-γ	Type II interferon receptor	T cells, NK cells	All cells	Regulates macrophage and NK cell activations. Stimulates immunoglobulin secretion by B cells. Induction of class II histocompatibility antigens. T_H1 T cell differentiation.
TNF-α	TNFrI, TNFrII	Monocytes-macrophages, mast cells, basophils, eosinophils, NK cells, B cells, T cells, keratinocytes, fibroblasts, thymic epithelial cells	All cells except erythrocytes	Fever, anorexia, shock, capillary leak syndrome, enhanced leukocyte cytotoxicity, enhanced NK cell function, acute phase protein synthesis, proinflammatory cytokine induction.

(*continued*)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (*CONTINUED*)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
TNF-β	TNFrI, TNFrII	T cells, B cells	All cells except erythrocytes	Cell cytotoxicity, lymph node and spleen development.
LT-β	LTβR	T cells	All cells except erythrocytes	Cell cytotoxicity, normal lymph node development
G-CSF	G-CSFr; gp130	Monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells, stromal cells	Myeloid cells, endothelial cells	Regulates myelopoiesis. Enhances survival and function of neutrophils. Clinical use in reversing neutropenia after cytotoxic chemotherapy.
GM-CSF	GM-CSFr, common β	T cells, monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells	Monocytes-macrophages, neutrophils, eosinophils, fibroblasts, endothelial cells	Regulates myelopoiesis. Enhances macrophage bactericidal and tumoricidal activity. Mediator of dendritic cell maturation and function. Upregulates NK cell function. Clinical use in reversing neutropenia after cytotoxic chemotherapy.
M-CSF	M-CSFr (*c-fms* protooncogene)	Fibroblasts, endothelial cells, monocytes-macrophages, T cells, B cells, epithelial cells including thymic epithelium	Monocytes-macrophages	Regulates monocyte-macrophage production and function.
LIF	LIFr; gp130	Activated T cells, bone marrow stromal cells, thymic epithelium	Megakaryocytes, monocytes, hepatocytes, possibly lymphocyte subpopulations	Induces hepatic acute-phase protein production. Stimulates macrophage differentiation. Promotes growth of myeloma cells and hematopoietic progenitors. Stimulates thrombopoiesis.
OSM	OSMr; LIFr; gp130	Activated monocytes-macrophages and T cells, bone marrow stromal cells, some breast carcinoma cell lines, myeloma cells	Neurons, hepatocytes, monocytes-macrophages, adipocytes, alveolar epithelial cells, embryonic stem cells, melanocytes, endothelial cells, fibroblasts, myeloma cells	Induces hepatic acute-phase protein production. Stimulates macrophage differentiation. Promotes growth of myeloma cells and hematopoietic progenitors. Stimulates thrombopoiesis. Stimulates growth of Kaposi's sarcoma cells.
SCF	SCFr (*c-kit* protooncogene)	Bone marrow stromal cells and fibroblasts	Embryonic stem cells, myeloid and lymphoid precursors, mast cells.	Stimulates hematopoietic progenitor cell growth, mast cell growth, promotes embryonic stem cell migration.
TGF-β (3 isoforms)	Type I, II, III TGF-β receptor	Most cell types	Most cell types	Downregulates T cell, macrophage, and granulocyte responses. Stimulates synthesis of matrix proteins. Stimulates angiogenesis.
Lymphotactin/SCM-1	Unknown	NK cells, mast cells, double negative thymocytes, activated CD8+ T cells	T cells, NK cells	Chemoattractant for lymphocytes. Only known chemokine of C class.
MCP-1	CCR2	Fibroblasts, smooth-muscle cells, activated PBMCs	Monocytes-macrophages, NK cells, memory T cells, basophils	Chemoattractant for monocytes, activated memory T cells, and NK cells. Induces granule release from CD8+ T cells and NK cells. Potent histamine-releasing factor for basophils. Suppresses proliferation of hematopoietic precursors. Regulates monocyte protease production.

(*continued*)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (*CONTINUED*)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
MCP-2	CCR1, CCR2	Fibroblasts, activated PBMCs	Monocytes-macrophages, T cells, eosinophils, basophils, NK cells	Chemoattractant for monocytes, memory and naïve T cells, eosinophils, ?NK cells. Activates basophils and eosinophils. Regulates monocyte protease production.
MCP-3	CCR1, CCR2	Fibroblasts, activated PBMCs	Monocytes-macrophages, T cells, eosinophils, basophils, NK cells, dendritic cells	Chemoattractant for monocytes, memory and naïve T cells, dendritic cells, eosinophils, ?NK cells. Activates basophils and eosinophils. Regulates monocyte protease production.
MCP-4	CCR2, CCR3	Lung, colon, small intestinal epithelial cells, activated endothelial cells	Monocytes-macrophages, T cells, eosinophils, basophils	Chemoattractant for monocytes, T cells, eosinophils, and basophils
Eotaxin	CCR3	Pulmonary epithelial cells, heart	Eosinophils, basophils	Potent chemoattractant for eosinophils and basophils. Induces allergic airways disease. Acts in concert with IL-5 to activate eosinophils. Antibodies to eotaxin inhibit airway inflammation.
TARC	CCR4	Thymus, dendritic cells, activated T cells	T cells, NK cells	Chemoattractant for T and NK cells.
MDC	CCR4	Monocytes-macrophages, dendritic cells, thymus	Activated T cells	Chemoattractant for activated T cells. Inhibits infection with T cell tropic HIV.
MIP-1α	CCR1, CCR5	Monocytes-macrophages, T cells	Monocytes-macrophages, T cells, dendritic cells, NK cells, eosinophils, basophils	Chemoattractant for monocytes, T cells, dendritic cells, NK cells, and weak chemoattractant for eosinophils and basophils. Activates NK cell function. Suppresses proliferation of hematopoietic precursors. Necessary for myocarditis associated with Coxsackie virus infection. Inhibits infection with monocytotropic HIV.
MIP-1β	CCR5	Monocytes-macrophages, T cells	Monocytes-macrophages, T cells, NK cells, dendritic cells	Chemoattractant for monocytes, T cells, and NK cells. Activates NK cell function. Inhibits infection with monocytotropic HIV.
RANTES	CCR1, CCR2, CCR5	Monocytes-macrophages, T cells, fibroblasts, eosinophils	Monocytes-macrophages, T cells, NK cells, dendritic cells, eosinophils, basophils	Chemoattractant for monocytes-macrophages, CD4+, CD45Ro+T cells, CD8+ T cells, NK cells, eosinophils, and basophils. Induces histamine release from basophils. Inhibits infections with monocytotropic HIV.
LARC/ MIP-3α/ Exodus-1	CCR6	Dendritic cells, fetal liver cells, activated T cells	T cells, B cells	Chemoattractant for lymphocytes.
ELC/MIP-3β	CCR7	Thymus, lymph node, appendix	Activated T cells and B cells	Chemoattractant for B and T cells. Receptor upregulated on EBV-infected B cells and HSV-infected T cells.

(*continued*)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (*CONTINUED*)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
I-309/TCA-3	CCR8	Activated T cells	Monocytes-macrophages, T cells	Chemoattractant for monocytes. Prevents glucocorticoid-induced apoptosis in some T cell lines.
SLC/TCA-4/ Exodus-2	Unknown	Thymic epithelial cells, lymph node, appendix and spleen	T cells	Chemoattractant for T lymphocytes. Inhibits hematopoiesis.
DC-CK1/ PARC	Unknown	Dendritic cells in secondary lymphoid tissues	Naïve T cells	May have a role in induction of immune responses.
TECK	Unknown	Dendritic cells, thymus, liver, small intestine	T cells, monocytes-macrophages, dendritic cells	Thymic dendritic cell–derived cytokine, possibly involved in T cell development
GRO-α/ MGSA	CXCR2	Activated granulocytes, monocyte-macrophages, and epithelial cells	Neutrophils, epithelial cells, ?endothelial cells	Neutrophil chemoattractant and activator. Mitogenic for some melanoma cell lines. Suppresses proliferation of hematopoietic precursors. Angiogenic activity.
GRO-β/ MIP-2α	CXCR2	Activated granulocytes and monocyte-macrophages	Neutrophils and ?endothelial cells.	Neutrophil chemoattractant and activator. Angiogenic activity.
NAP-2	CXCR2	Platelets	Neutrophils, basophils	Derived from platelet basic protein. Neutrophil chemoattractant and activator.
IP-10	CXCR3	Monocytes-macrophages, T cells, fibroblasts, endothelial cells, epithelial cells	Activated T cells, tumor-infiltrating lymphocytes, ?endothelial cells, ?NK cells	IFN-γ-inducible protein that is a chemoattractant for T cells. Suppresses proliferation of hematopoietic precursors.
MIG	CXCR3	Monocytes-macrophages, T cells, fibroblasts	Activated T cells, tumor-infiltrating lymphocytes	IFN-γ-inducible protein that is a chemoattractant for T cells. Suppresses proliferation of hematopoietic precursors.
SDF-1	CXCR4	Fibroblasts	T cells, dendritic cells, ?basophils, ?endothelial cells	Low-potency, high-efficacy T cell chemoattractant. Required for B-lymphocyte development. Prevents infection of CD4+, CXCR4+ cells by T cell tropic HIV.
Fractalkine	CX3CR1	Activated endothelial cells	NK cells, T cells,monocytes-macrophages	Cell-surface chemokine/mucin hybrid molecule that functions as a chemoattractant, leukocyte activator, and cell adhesion molecule.
PF-4	Unknown	Platelets, megakaryocytes	Fibroblasts, endothelial cells	Chemoattractant for fibroblasts. Suppresses proliferation of hematopoietic precursors. Inhibits endothelial cell proliferation and angiogenesis.

Abbreviations: IL, interleukin; NK, natural killer; T_H1 and T_H2, helper T cell subsets; Ig, immunoglobulin; CXCR, CXC-type chemokine receptor; B7-1, CD80, B7-2, CD86; PBMC, peripheral blood mononuclear cells; VCAM, vascular cell adhesion molecule; IFN, interferon; MHC, major histocompatibility complex; TNF, tumor necrosis factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage CSF; M-CSF, macrophage CSF; LIF, leukemia inhibitory factor; OSM, oncostatin M; SCF, stem cell factor; TGF, transforming growth factor; MCP, monocyte chemotactic protein; CCR, CC-type chemokine receptor; TARC, thymus- and activation-regulated chemokine; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normally T cell–expressed and –secreted; LARC, liver- and activation-regulated chemokine; EBV, Epstein-Barr virus; ELC, EB11 ligand chemokine (MIP-1b); HSV, herpes simplex virus; TCA, T-cell activation protein; DC-CK, dendritic cell chemokine; PARC, pulmonary- and activation-regulated chemokine; SLC, secondary lymphoid tissue chemokine; TECK, thymus expressed chemokine; GRP, growth-related peptide; MGSA, melanoma growth-stimulating activity; NAP, neutrophil-activating protein; IP-10, IFN-γ-inducible protein-10; MIG, monokine induced by IFN-γ; SDF, stromal cell-derived factor; PF, platelet factor.

Source: Data from JS Sundy et al: Appendix B, in *Inflammation, Basic Principles and Clinical Correlates*, 3rd ed, J Gallin and R Snyderman (eds). Philadelphia, Lippincott Williams and Wilkins, 1999.

TABLE 1-8

CC, CXC_1, CX_3, C_1 AND XC FAMILIES OF CHEMOKINES AND CHEMOKINE RECEPTORS

CHEMOKINE RECEPTOR	CHEMOKINE LIGANDS	CELL TYPES	DISEASE CONNECTION
CCR1	CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), CCL14 (HCC1)	T cells, monocytes, eosinophils, basophils	Rheumatoid arthritis, multiple sclerosis
CCR2	CCL2 (MCP-1), CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP-4), CCL16 (HCC4)	Monocytes, dendritic cells (immature), memory T cells	Atherosclerosis, rheumatoid arthritis, multiple sclerosis, resistance to intracellular pathogens, type 2 diabetes mellitus
CCR3	CCL11 (eotaxin), CCL13 (eotaxin-2), CCL7 (MCP-3), CCL5 (RANTES), CCL8 (MCP-2), CCL13 (MCP-4)	Eosinophils, basophils, mast cells, T_H2, platelets	Allergic asthma and rhinitis
CCR4	CCL17 (TARC), CCL22 (MDC)	T cells (T_H2) dendritic cells (mature), basophils, macrophages, platelets	Parasitic infection, graft rejection, T cell homing to skin
CCR5	CCL3 (MIP-1α), CCL4 (MIP-1α), CCL5 (RANTES), CCL11 (eotaxin), CCL14 (HCC1), CCL16 (HCC4)	T cells, monocytes	HIV-1 co-receptor (T cell–tropic strains), transplant rejection
CCR6	CCL20 (MIP-3α, LARC)	T cells (T regulatory and memory), B cells, dendritic cells	Mucosal humoral immunity, allergic asthma, intestinal T cell homing
CCR7	CCL19 (ELC), CCL21 (SLC)	T cells, dendritic cells (mature)	Transport of T cells and dendritic cells to lymph nodes, antigen presentation, and cellular immunity
CCR8	CCL1 (1309)	T cells (T_H2), monocytes, dendritic cells	Dendritic cell migration to lymph node, type 2 cellular immunity, granuloma formation
CCR9	CCL25 (TECK)	T cells, IgA+ plasma cells	Homing of T cells and IgA+ plasma cells to the intestine, inflammatory bowel disease
CCR10	CCL27 (CTACK), CCL28 (MEC)	T cells	T cell homing to intestine and skin
CXCR1	CXCL8 (interleukin-8), CXCL6 (GCP2)	Neutrophils, monocytes	Inflammatory lung disease, COPD
CXCR2	CXCL8, CXCL1 (GROα), CXCL2 (GROα), CXCL3 (GROα), CXCL5 (ENA-78), CXCL6	Neutrophils, monocytes, microvascular endothelial cells	Inflammatory lung disease, COPD, angiogenic for tumor growth
CXCR3-A	CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC)	Type 1 helper cells, mast cells, mesangial cells	Inflammatory skin disease, multiple sclerosis, transplant rejection
CXCR3-B	CXCL4 (PF4), CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC)	Microvascular endothelial cells, neoplastic cells	Angiostatic for tumor growth
CXCR4	CXCL12 (SDF-1)	Widely expressed	HIV-1 co-receptor (T cell–tropic), tumor metastases, hematopoiesis
CXCR5	CXCL13 (BCA-1)	B cells, follicular helper T cells	Formation of B cell follicles
CXCR6	CXCL16 (SR-PSOX)	CD8+ T cells, natural killer cells, and memory CD4+ T cells	Inflammatory liver disease, atherosclerosis (CXCL16)
CX_3CR1	CX3CL1 (fractalkine)	Macrophages, endothelial cells, smooth-muscle cells	Atherosclerosis
XCR1	XCL1 (lymphotactin), XCL2	T cells, natural killer cells	Rheumatoid arthritis, IgA nephropathy, tumor response

Abbreviations: MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; HCC, hemofiltrate chemokine; T_H2, type 2 helper T cells; TARC, thymus- and activation-regulated chemokine; MDC, macrophage-derived chemokine; LARC, liver- and activation-regulated chemokine; ELC, Epstein-Barr I1-ligand chemokine; SLC, secondary lymphoid-tissue chemokine; TECK, thymus-expressed chemokine; CTACK, cutaneous T cell–attracting chemokine; MEC, mammary-enriched chemokine; GCP, granulocyte chemotactic protein; COPD, chronic obstructive pulmonary disease; GRO, growth-regulated oncogene; ENA, epithelial-cell–derived neutrophil-activating peptide; MIG, monokine induced by interferon-γ IP-10, interferon inducible 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; PF, platelet factor; SDF, stromal-cell–derived factor; BCA-1, B-cell chemoattractant 1; SR-PSOX, scavenger receptor for phosphatidylserine-containing oxidized lipids.

Source: From IF Charo, RM Ranshohoff: N Engl J Med 354:610, 2006, with permission. Copyright Massachusetts Medical Society. All rights reserved.

TABLE 1-9

MAJOR STRUCTURAL FAMILIES OF CYTOKINES	
Four α-helix-bundle family interleukins	Interleukin-2 (IL-2) Subfamily: Interleukins: IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, IL-21, IL-23 Not called interleukins: Colony-stimulating factor-1 (CSF1), granulocyte–macrophage colony-stimulating factor (CSF2), Flt-3 ligand, erythropoietin (EPO), thrombopoietin (THPO), leukocyte inhibitory factor (LIF) Not interleukins: Growth hormone (GH1), prolactin (PRL), leptin (LEP), cardiotrophin (CTF1), ciliary neurotrophic factor (CNTF), cytokine receptor-like factor 1 (CLC or CLF) Interferon (IFN) subfamily: IFN-β, IFN-α IL-10 subfamily: IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26
IL-1 family	IL-1α (IL1A), IL-1β (IL1B), IL-18 (IL18), and paralogues, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F
Chemokines	IL-8, MCP-1, MCP-2, MCP-3, MCP-4, eotaxin, TARC, LARC/MIP-3α, MDC, MIP-1α, MIP-1β, RANTES, MIP-3β, I-309, SLC, PARC, TECK, GROα, GROβ, NAP-2, IP-19, MIG, SDF-1, PF4

Abbreviations: GRO, growth-related peptide; IL, interleukin; IP, INF-γ-inducible protein; LARC, liver- and activation-regulated chemokine; MCP, monocyte chemotactic protein; MDC, macrophage-derived chemokine; MIG, monokine induced by IFN-γ; MIP, macrophage inflammatory protein; NAP, neutrophil-activating protein; PARC, pulmonary- and activation-regulated chemokine; PF4, platelet factor; RANTES, regulated on activation, normally T cell–expressed and –secreted; SDF, stromal cell–derived factor; SLC, secondary lymphoid tissue.
Source: Adapted from JW Schrader: Trends Immunol 23:573, 2002. Copyright 2002, with permission from Elsevier.

activate cells of the adaptive immune system and, like TLR stimulation, by a variety of factors, determine the type and quality of the adaptive immune response that is triggered (Table 1-4).

Large granular lymphocytes/natural killer cells

Large granular lymphocytes (LGLs) or NK cells account for ~5–15% of peripheral blood lymphocytes. NK cells are nonadherent, nonphagocytic cells with large azurophilic cytoplasmic granules. NK cells express surface receptors for the Fc portion of IgG (CD16) and for NCAM-I (CD56), and many NK cells express T lineage markers, particularly CD8, and proliferate in response to IL-2. NK cells arise in both bone marrow and thymic microenvironments.

Functionally, NK cells share features with both monocytes- macrophages and neutrophils in that they mediate both antibody-dependent cellular cytotoxicity (ADCC) and NK cell activity. ADCC is the binding of an opsonized (antibody-coated) target cell to an Fc receptor–bearing effector cell via the Fc region of

TABLE 1-10

CYTOKINE FAMILIES GROUPED BY STRUCTURAL SIMILARITY	
Hematopoietins	IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, IL-16, IL-17, IL-21, IL-23, EPO, LIF, GM-CSF, G-CSF, OSM, CNTF, GH, and TPO TNF-α, LT-α, LT-β, CD40L, CD30L, CD27L, 4-1BBL, OX40, OPG, and FasL
IL-1	IL-1α, IL-1β, IL-1ra, IL-18, bFGF, aFGF, and ECGF
PDGF	PDGF A, PDGF B, and M-CSF
TGF-β	TGF-β and BMPs (1,2,4 etc.)
C-X-C chemokines	IL-8, Gro-α/β/γ, NAP-2, ENA78, GCP-2, PF4, CTAP-3, MIG, and IP-10
C-C chemokines	MCP-1, MCP-2, MCP-3, MIP-1α, MIP-1β, RANTES

Abbreviations: aFGF, acidic fibroblast growth factor; 4-1BBL, 401 BB ligand; bFGF, basic fibroblast growth factor; BMP, bone marrow morphogenetic proteins; C-C, cysteine-cysteine; CD, cluster of differentiation; CNTF, ciliary neurotrophic factor; CTAP, connective tissue–activating peptide; C-X-C, cysteine-x-cysteine; ECGF, endothelial cell growth factor; EPO, erythropoietin; FasL, Fas ligand; GCP-2, granulocyte chemotactic protein 2; G-CSF, granulocyte colony-stimulating factor; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gro, growth-related gene products; IFN, interferon; IL, interleukin; IP, interferon-γ inducible protein; LIF, leukemia inhibitory factor; LT, lymphotoxin; MCP, monocyte chemoattractant; M-CSF, macrophage colony-stimulating factor; MIG, monokine induced by interferon-γ; MIP, macrophage inflammatory protein; NAP-2, neutrophil activating protein 2; OPG, osteoprotegerin; OSM, oncostatin M; PDGF, platelet-derived growth factor; PF, platelet factor; R, receptor; RANTES, regulated on activation, normal T cell–expressed and –secreted; TGF, transforming growth factor; TNF, tumor necrosis factor; TPO, thyroperoxidase.

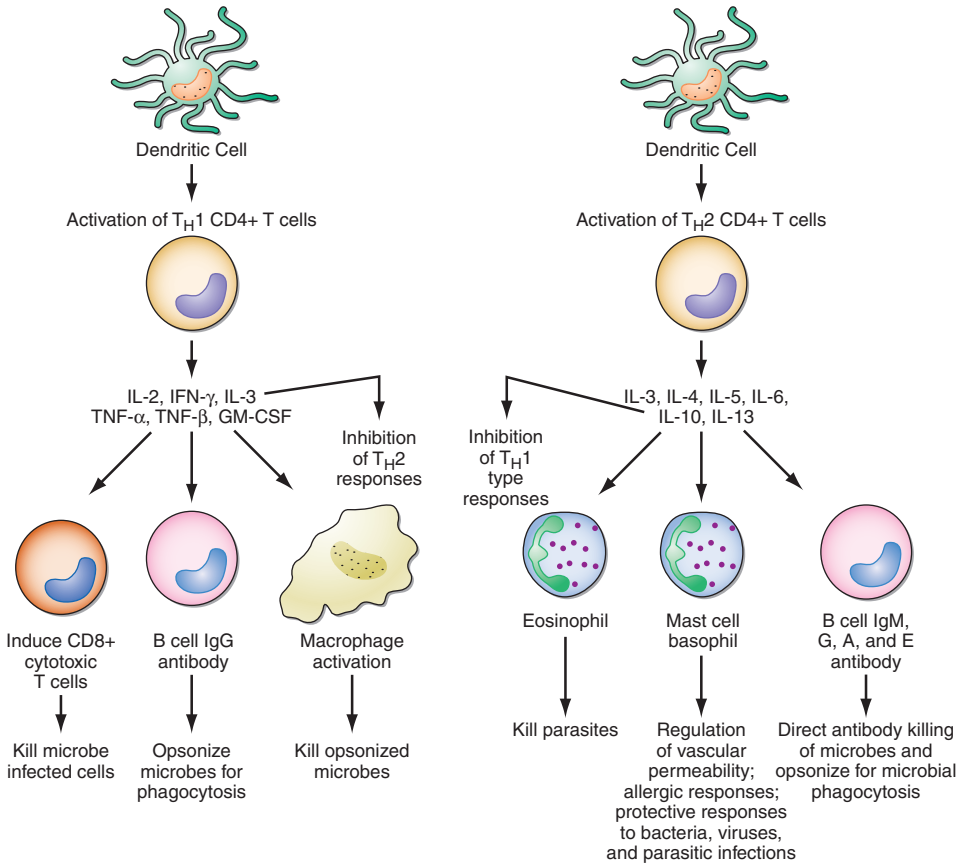


FIGURE 1-3

CD4+ helper T1 (T_H1) cells and T_H2 T cells secrete distinct but overlapping sets of cytokines. T_H1 CD4+ cells are frequently activated in immune and inflammatory reactions against intracellular bacteria or viruses, while T_H2 CD4+ cells are frequently activated for certain types of antibody production against parasites and extracellular encapsulated bacteria; they are also activated in allergic diseases. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor. (*Adapted from S Romagnani: CD4 effector cells, in Inflammation: Basic Principles and Clinical Correlates, 3rd ed, J Gallin, R Synderman (eds). Philadelphia, Lippincott Williams & Wilkins, 1999, pp 177; with permission.*)

antibody, resulting in lysis of the target by the effector cell. NK cell cytotoxicity is the nonimmune (i.e., effector cell never having had previous contact with the target), MHC-unrestricted, non-antibody-mediated killing of target cells, which are usually malignant cell types, transplanted foreign cells, or virus-infected cells. Thus, NK cell cytotoxicity may play an important role in immune surveillance and destruction of malignant and virally infected host cells. NK cell hyporesponsiveness is also observed in patients with *Chédiak-Higashi syndrome*, an autosomal recessive disease associated with fusion of cytoplasmic granules and defective degranulation of neutrophil lysosomes.

NK cells have a variety of surface receptors that have inhibitory or activating functions and belong to two structural families. These families include the immunoglobulin superfamily and the lectin-like type II transmembrane proteins. NK immunoglobulin superfamily receptors include the killer cell immunoglobulin-like activating or inhibitory receptors (KIRs), many of which have been shown to have HLA class I ligands. The KIRs are made up proteins with either two (KIR2D) or three (KIR3D) extracellular immunoglobulin domains (D). Moreover, their nomenclature designates their function as either inhibitory KIRs with a long (L) cytoplasmic tail and immunoreceptor tyrosine-based inhibitory motif (ITIM) (KIRDL) or activating KIRs with a short (S) cytoplasmic tail (KIRDS). NK cell inactivation by KIRs is a central mechanism to prevent damage to normal host cells. Genetic studies have demonstrated the association of KIRs with viral infection outcome and autoimmune disease **(Table 1-11)**.

In addition to the KIRs, a second set of immunoglobulin superfamily receptors include the natural cytotoxicity receptors (NCRs), which include NKp46, NKp30, and NKp44. These receptors help to mediate NK cell activation against target cells. The ligands to which NCRs bind on target cells remain largely undefined.

NK cell signaling is, therefore, a highly coordinated series of inhibiting and activating signals that prevent NK cells from responding to uninfected, nonmalignant

TABLE 1-11

ASSOCIATION OF KIRS WITH DISEASE

DISEASE	KIR ASSOCIATION	OBSERVATION
Psoriatic arthritis	KIR2DS1/KIR2DS2; HLA-Cw group homozygosity	Susceptibility
Spondylarthritides	Increased KIR3DL2 expression Interaction HLA-B27 homodimers with KIR3DL1/KIR3DL2; independent of peptide	May contribute to disease pathology May contribute to disease pathogenesis
Ankylosing spondylitis	KIR3DL1/3DS1; HLA B27 genotypes	Susceptibility
Rheumatoid vasculitis	KIR2DS2; HLA-Cw*03 Increased KIR2L2/2DS2 in patients with extra articular manifestations	Susceptibility Clinical manifestations may have different genetic backgrounds with respect to KIR genotype
Rheumatoid arthritis	Decreased KIR2DS1/3DS1 in patients without bone erosions KIR2DS4; HLA-Cw4	Susceptibility Susceptibility
Scleroderma	KIR2DS2+/KIR2DL2-	Susceptibility
Behçet's disease	Altered KIR3DL1 expression	Associated with severe eye disease
Psoriasis vulgaris	2DS1; HLA-Cw*06 2DS1; 2DL5; Haplotype B	Susceptibility Susceptibility
IDDM	KIR2DS2; HLA-C1	Susceptibility
Type 1 diabetes	KIR2DS2; HLA-C1 and no HLA-C2, no HLA-Bw4	Increased disease progression
Preeclampsia	KIR2DL1 with fewer KIR2DS (mother); HLA-C2 (fetus)	Increased disease progression
AIDS	KIR3DS1; HLA-Bw4Ile80 KIR3DS1 homozygous; No HLA-Bw4Ile^{80}	Decreased disease progression Increased disease progression
HCV infection	KIR2DL3 homozygous; HLA-C1 homozygous	Decreased disease progression
Cervical neoplasia (HPV induced)	KIR3DS1; HLA-C1 homozygous and no HLA-Bw4	Increased disease progression
Malignant melanoma	KIR2DL2 and/or KIR2DL3; HLA-C1	Increased disease progression

Abbreviations: HCV, hepatitis C virus; HLA, human leukocyte antigen; HPV, human papillomavirus; IDDM, insulin-dependent diabetes mellitus; KIR, killer cell immunoglobulin-like receptor.
Source: Adapted from R Diaz-Pena et al: Adv Exp Med Biol 649:286, 2009.

self-cells; however, they are activated to attack malignant and virally infected cells **(Fig. 1-4)**. Recent evidence suggests that NK cells, although not possessing rearranging immune recognition genes, may be able to mediate recall for NK cell responses to viruses and for immune responses such as contact hypersensitivity.

Some NK cells express CD3 and invariant T cell receptor (TCR) alpha chains and are termed *NK T cells*. TCRs of NK T cells recognize lipid molecules of intracellular bacteria when presented in the context of CD1d molecules on APCs. Upon activation, NK T cells secrete effector cytokines such as IL-4 and IFNγ. This mode of recognition of intracellular bacteria such as *Listeria monocytogenes* and *Mycobacterium tuberculosis* by NK T cells leads to induction of activation of DCs and is thought to be an important innate defense mechanism against these organisms.

Neutrophils, eosinophils, and basophils

Granulocytes are present in nearly all forms of inflammation and are amplifiers and effectors of innate immune responses (Figs. 1-2 and 1-3). Unchecked accumulation and activation of granulocytes can lead to host tissue damage, as seen in neutrophil- and eosinophil-mediated *systemic necrotizing vasculitis*. Granulocytes are derived from stem cells in bone marrow. Each type of granulocyte (neutrophil, eosinophil, or basophil) is

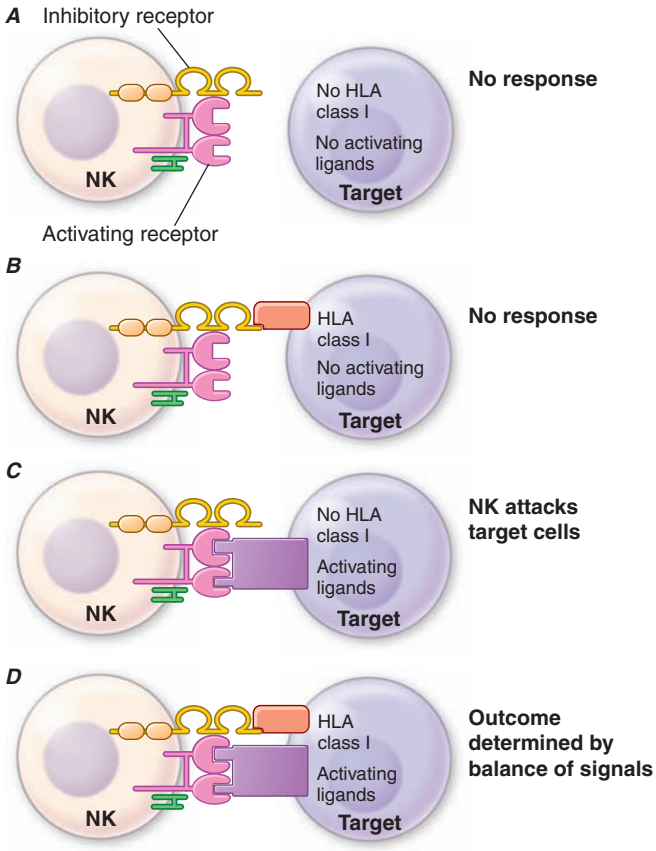


FIGURE 1-4

Encounters between NK cells: potential targets and possible outcomes. The amount of activating and inhibitory receptors on the NK cells and the amount of ligands on the target cell, as well as the qualitative differences in the signals transduced, determine the extent of the NK response. ***A.*** When target cells have no HLA class I nor activating ligands, NK cells cannot kill target cells. ***B.*** When target cells bear self-HLA, NK cells cannot kill targets. ***C.*** When target cells are pathogen infected and have downregulated HLA and express activating ligands, NK cells kill target cells. ***D.*** When NK cells encounter targets with both self-HLA and activating receptors, then the level of target killing is determined by the balance of inhibitory and activating signals to the NK cell. HLA, human leukocyte antigen; NK, natural killer. (*Adapted from Lanier; reproduced with permission from Annual Reviews Inc. Copyright 2011 by Annual Reviews Inc.*)

derived from a different subclass of progenitor cell that is stimulated to proliferate by colony-stimulating factors (Table 1-7). During terminal maturation of granulocytes, class-specific nuclear morphology and cytoplasmic granules appear that allow for histologic identification of granulocyte type.

Neutrophils express Fc receptors for IgG (CD16) and receptors for activated complement components (C3b or CD35). Upon interaction of neutrophils with opsonized bacteria or immune complexes, azurophilic granules (containing myeloperoxidase, lysozyme, elastase, and other enzymes) and specific granules (containing lactoferrin, lysozyme, collagenase, and other enzymes) are released, and microbicidal superoxide radicals (O_2^-) are generated at the neutrophil surface. The generation of superoxide leads to inflammation by direct injury to tissue and by alteration of macromolecules such as collagen and DNA.

Eosinophils express Fc receptors for IgG (CD32) and are potent cytotoxic effector cells for various parasitic organisms. In *Nippostrongylus brasiliensis* helminth infection, eosinophils are important cytotoxic effector cells for removal of these parasites. Key to regulation of eosinophil cytotoxicity to *N. brasiliensis* worms are antigen-specific T helper cells that produce IL-4, thus providing an example of regulation of innate immune responses by adaptive immunity antigen-specific T cells. Intracytoplasmic contents of eosinophils, such as major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin, are capable of directly damaging tissues and may be responsible in part for the organ system dysfunction in the *hypereosinophilic syndromes*. Since the eosinophil granule contains anti-inflammatory types of enzymes (histaminase, arylsulfatase, phospholipase D), eosinophils may homeostatically downregulate or terminate ongoing inflammatory responses.

Basophils and tissue mast cells are potent reservoirs of cytokines such as IL-4 and can respond to bacteria and viruses with antipathogen cytokine production through multiple TLRs expressed on their surface. Mast cells and basophils can also mediate immunity through the binding of antipathogen antibodies. This is a particularly important host defense mechanism against parasitic diseases. Basophils express high-affinity surface receptors for IgE (FcRI) and, upon cross-linking of basophil-bound IgE by antigen, can release histamine, eosinophil chemotactic factor of anaphylaxis, and neutral protease—all mediators of allergic immediate (anaphylaxis) hypersensitivity responses **(Table 1-12)**. In addition, basophils express surface receptors for activated complement components (C3a, C5a), through which mediator release can be directly effected. Thus, basophils, like most cells of the immune system, can be activated in the service of host defense against pathogens, or they can be activated for mediation release and cause pathogenic responses in allergic and inflammatory diseases.

The complement system

The complement system, an important soluble component of the innate immune system, is a series of plasma enzymes, regulatory proteins, and proteins that are activated in a cascading fashion, resulting in cell lysis. There are four pathways of the complement system: the classic activation pathway activated by antigen/antibody

TABLE 1-12

EXAMPLES OF MEDIATORS RELEASED FROM HUMAN CELLS AND BASOPHILS

MEDIATOR	ACTIONS
Histamine	Smooth-muscle contraction, increased vascular permeability
Slow reacting substance of anaphylaxis (SRSA) (leukotriene C4, D4, E4)	Smooth-muscle contraction
Eosinophil chemotactic factor of anaphylaxis (ECF-A)	Chemotactic attraction of eosinophils
Platelet-activating factor	Activates platelets to secrete serotonin and other mediators: smooth-muscle contraction; induces vascular permeability
Neutrophil chemotactic factor (NCF)	Chemotactic attraction of neutrophils
Leukotactic activity (leukotriene B4)	Chemotactic attraction of neutrophils
Heparin	Anticoagulant
Basophil kallikrein of anaphylaxis (BK-A)	Cleaves kininogen to form bradykinin

immune complexes, the MBL (a serum collectin; Table 1-3) activation pathway activated by microbes with terminal mannose groups, the alternative activation pathway activated by microbes or tumor cells, and the terminal pathway that is common to the first three pathways and leads to the membrane attack complex that lyses cells **(Fig. 1-5)**. The series of enzymes of the complement system are serine proteases.

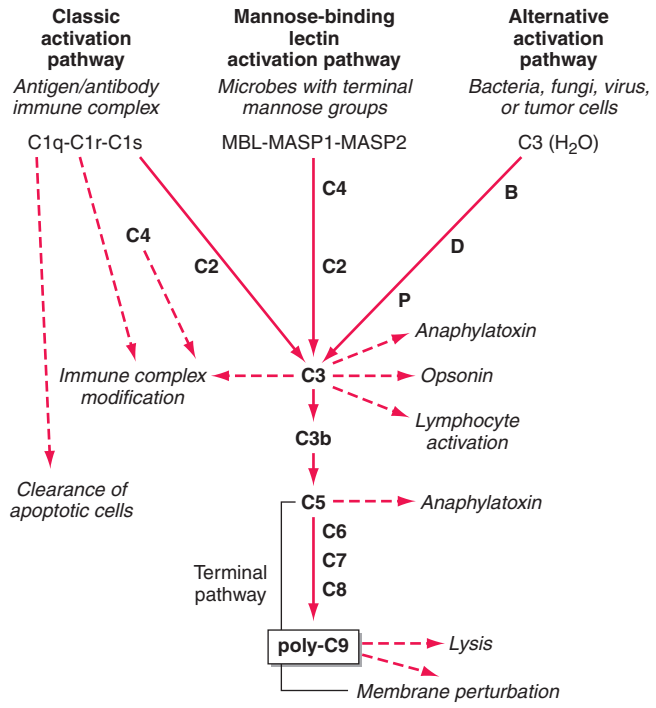


FIGURE 1-5

The four pathways and the effector mechanisms of the complement system. Dashed arrows indicate the functions of pathway components. (*After BJ Morley, MJ Walport: The Complement Facts Books. London, Academic Press, 2000; with permission. Copyright Academic Press, London, 2000.*)

Activation of the classic complement pathway via immune complex binding to C1q links the innate and adaptive immune systems via specific antibody in the immune complex. The alternative complement activation pathway is antibody-independent and is activated by binding of C3 directly to pathogens and "altered self" such as tumor cells. In the renal glomerular inflammatory disease *IgA nephropathy*, IgA activates the alternative complement pathway and causes glomerular damage and decreased renal function. Activation of the classic complement pathway via C1, C4, and C2 and activation of the alternative pathway via factor D, C3, and factor B both lead to cleavage and activation of C3. C3 activation fragments, when bound to target surfaces such as bacteria and other foreign antigens, are critical for opsonization (coating by antibody and complement) in preparation for phagocytosis. The MBL pathway substitutes MBL-associated serine proteases (MASPs) 1 and 2 for C1q, C1r, and C1s to activate C4. The MBL activation pathway is activated by mannose on the surface of bacteria and viruses.

The three pathways of complement activation all converge on the final common terminal pathway. C3 cleavage by each pathway results in activation of C5, C6, C7, C8, and C9, resulting in the membrane attack complex that physically inserts into the membranes of target cells or bacteria and lyses them.

Thus, complement activation is a critical component of innate immunity for responding to microbial infection. The functional consequences of complement activation by the three initiating pathways and the terminal pathway are shown in Fig. 1-5. In general the cleavage products of complement components facilitate microbe or damaged cell clearance (C1q, C4, C3), promote activation and enhancement of inflammation (anaphylatoxins, C3a, C5a), and promote microbe or opsonized cell lysis (membrane attack complex).

CYTOKINES

Cytokines are soluble proteins produced by a wide variety of hematopoietic and nonhematopoietic cell types (Tables 1-7 to 1-10). They are critical for both normal innate and adaptive immune responses, and their expression may be perturbed in most immune, inflammatory, and infectious disease states.

Cytokines are involved in the regulation of the growth, development, and activation of immune system cells and in the mediation of the inflammatory response. In general, cytokines are characterized by considerable redundancy; different cytokines have similar functions. In addition, many cytokines are pleiotropic in that they are capable of acting on many different cell types. This pleiotropism results from the expression on multiple cell types of receptors for the same cytokine (discussed later), leading to the formation of "cytokine networks." The action of cytokines may be (1) autocrine when the target cell is the same cell that secretes the cytokine, (2) paracrine when the target cell is nearby, and (3) endocrine when the cytokine is secreted into the circulation and acts distal to the source.

Cytokines have been named based on presumed targets or based on presumed functions. Those cytokines that are thought to primarily target leukocytes have been named interleukins (IL-1, -2, -3, etc.). Many cytokines that were originally described as having a certain function have retained those names (granulocyte colony-stimulating factor or G-CSF, etc.). Cytokines belong in general to three major structural families: the hematopoietin family; the TNF, IL-1, platelet-derived growth factor (PDGF), and transforming growth factor (TGF) β families; and the CXC and C-C chemokine families (Table 1-10). Chemokines are cytokines that regulate cell movement and trafficking; they act through G protein–coupled receptors and have a distinctive three-dimensional structure. IL-8 is the only chemokine that early on was named an interleukin (Table 1-7).

In general, cytokines exert their effects by influencing gene activation that results in cellular activation, growth, differentiation, functional cell-surface molecule expression, and cellular effector function. In this regard, cytokines can have dramatic effects on the regulation of immune responses and the pathogenesis of a variety of diseases. Indeed, T cells have been categorized on the basis of the pattern of cytokines that they secrete, which results in either humoral immune response (T_H2) or cell-mediated immune response (T_H1). A third type of T helper cell is the T_H17 cell that contributes to host defense against extracellular bacteria and fungi, particularly at mucosal sites (Fig. 1-2).

Cytokine receptors can be grouped into five general families based on similarities in their extracellular amino acid sequences and conserved structural domains. The *immunoglobulin (Ig) superfamily* represents a large number of cell-surface and secreted proteins. The IL-1 receptors (type 1, type 2) are examples of cytokine receptors with extracellular Ig domains.

The hallmark of the *hematopoietic growth factor (type 1) receptor* family is that the extracellular regions of each receptor contain two conserved motifs. One motif, located at the N terminus, is rich in cysteine residues. The other motif is located at the C terminus proximal to the transmembrane region and comprises five amino acid residues, tryptophan-serine-X-tryptophan-serine (WSXWS). This family can be grouped on the basis of the number of receptor subunits they have and on the utilization of shared subunits. A number of cytokine receptors, i.e., IL-6, IL-11, IL-12, and leukemia inhibitory factor, are paired with gp130. There is also a common 150-kDa subunit shared by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors. The gamma chain (γ_c) of the IL-2 receptor is common to the IL-2, IL-4, IL-7, IL-9, and IL-15 receptors. Thus, the specific cytokine receptor is responsible for ligand-specific binding, while the subunits such as gp130, the 150-kDa subunit, and γ_c are important in signal transduction. The γ_c gene is on the X chromosome, and mutations in the γ_c protein result in the *X-linked form of severe combined immune deficiency syndrome (X-SCID)*.

The members of the *interferon (type II) receptor* family include the receptors for IFN-γ and -β, which share a similar 210-amino-acid binding domain with conserved cysteine pairs at both the amino and carboxy termini. The members of the *TNF (type III) receptor family* share a common binding domain composed of repeated cysteine-rich regions. Members of this family include the p55 and p75 receptors for TNF (TNF-R1 and TNF-R2, respectively); CD40 antigen, which is an important B cell–surface marker involved in immunoglobulin isotype switching; fas/Apo-1, whose triggering induces apoptosis; CD27 and CD30, which are found on activated T cells and B cells; and nerve growth factor receptor.

The common motif for the *seven transmembrane helix family* was originally found in receptors linked to GTP-binding proteins. This family includes receptors for chemokines (Table 1-8), β-adrenergic receptors, and retinal rhodopsin. It is important to note that two members of the chemokine receptor family, CXC chemokine receptor type 4 (CXCR4) and β chemokine receptor type 5 (CCR5), have been found to serve as the two major co-receptors for binding and entry of HIV into CD4-expressing host cells.

Significant advances have been made in defining the signaling pathways through which cytokines exert their effects intracellularly. The Janus family of protein tyrosine kinases (JAK) is a critical element involved in signaling via the hematopoietin receptors. Four JAK

kinases, JAK1, JAK2, JAK3, and Tyk2, preferentially bind different cytokine receptor subunits. Cytokine binding to its receptor brings the cytokine receptor subunits into apposition and allows a pair of JAKs to transphosphorylate and activate one another. The JAKs then phosphorylate the receptor on the tyrosine residues and allow signaling molecules to bind to the receptor, where these molecules become phosphorylated. Signaling molecules bind the receptor because they have domains (SH2, or src homology 2 domains) that can bind phosphorylated tyrosine residues. There are a number of these important signaling molecules that bind the receptor, such as the adapter molecule SHC, which can couple the receptor to the activation of the mitogen-activated protein kinase pathway. In addition, an important class of substrate of the JAKs is the signal transducers and activators of transcription (STAT) family of transcription factors. STATs have SH2 domains that enable them to bind to phosphorylated receptors, where they are then phosphorylated by the JAKs. It appears that different STATs have specificity for different receptor subunits. The STATs then dissociate from the receptor and translocate to the nucleus, bind to DNA motifs that they recognize, and regulate gene expression. The STATs preferentially bind DNA motifs that are slightly different from one another and thereby control transcription of specific genes. The importance of this pathway is particularly relevant to lymphoid development. Mutations of JAK3 itself also result in a disorder identical to X-SCID; however, since JAK3 is found on chromosome 19 and not on the X chromosome, JAK3 deficiency occurs in boys and girls.

THE ADAPTIVE IMMUNE SYSTEM

Adaptive immunity is characterized by antigen-specific responses to a foreign antigen or pathogen. A key feature of adaptive immunity is that following the initial contact with antigen (*immunologic priming*), subsequent antigen exposure leads to more rapid and vigorous immune responses (*immunologic memory*). The adaptive immune system consists of dual limbs of cellular and humoral immunity. The principal effectors of cellular immunity are T lymphocytes, while the principal effectors of humoral immunity are B lymphocytes. Both B and T lymphocytes derive from a common stem cell **(Fig. 1-6)**.

The proportion and distribution of immunocompetent cells in various tissues reflect cell traffic, homing patterns, and functional capabilities. Bone marrow is the major site of maturation of B cells, monocytes-macrophages, dendritic cells, and granulocytes and contains pluripotent stem cells that, under the influence of various colony-stimulating factors, are capable of giving rise to all hematopoietic cell types. T cell precursors also arise from hematopoietic stem cells and home to the thymus for maturation. Mature T lymphocytes, B lymphocytes, monocytes, and dendritic cells enter the circulation and home to peripheral lymphoid organs (lymph nodes, spleen) and mucosal surface-associated lymphoid tissue (gut, genitourinary, and respiratory tracts) as well as the skin and mucous membranes and await activation by foreign antigen.

T cells

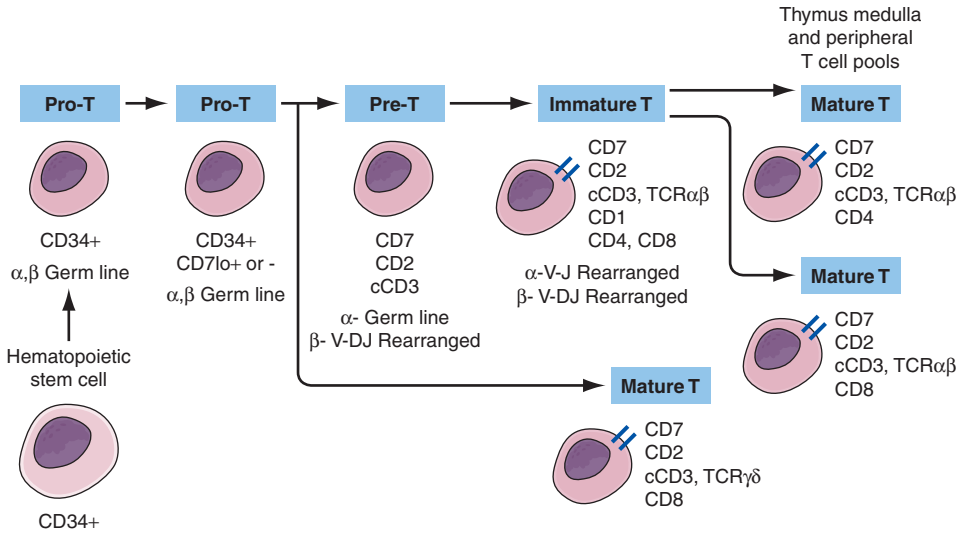
The pool of effector T cells is established in the thymus early in life and is maintained throughout life both by new T cell production in the thymus and by antigen-driven expansion of virgin peripheral T cells into "memory" T cells that reside in peripheral lymphoid organs. The thymus exports ~2% of the total number of thymocytes per day throughout life, with the total number of daily thymic emigrants decreasing by ~3% per year during the first four decades of life.

Mature T lymphocytes constitute 70–80% of normal peripheral blood lymphocytes (only 2% of the total-body lymphocytes are contained in peripheral blood), 90% of thoracic duct lymphocytes, 30–40% of lymph node cells, and 20–30% of spleen lymphoid cells. In lymph nodes, T cells occupy deep paracortical areas around B cell germinal centers, and in the spleen, they are located in periarteriolar areas of white pulp. T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into CD8+ cytotoxic T cells capable of lysis of virus-infected or foreign cells (short-lived effector T cells). Two populations of long-lived memory T cells are triggered by infections: effector memory and central memory T cells. Effector memory T cells reside in nonlymphoid organs and respond rapidly to repeated pathogenic infections with cytokine production and cytotoxic functions to kill virus-infected cells. Central memory T cells home to lymphoid organs where they replenish long- and short-lived and effector memory T cells as needed.

In general, CD4+ T cells are also the primary regulatory cells of T and B lymphocyte and monocyte function by the production of cytokines and by direct cell contact (Fig. 1-2). In addition, T cells regulate erythroid cell maturation in bone marrow and, through cell contact (CD40 ligand), have an important role in activation of B cells and induction of Ig isotype switching.

Human T cells express cell-surface proteins that mark stages of intrathymic T cell maturation or identify specific functional subpopulations of mature T cells. Many of these molecules mediate or participate in important T cell functions (Table 1-1, Fig. 1-6).

The earliest identifiable T cell precursors in bone marrow are CD34+ pro-T cells (i.e., cells in which TCR genes are neither rearranged nor expressed). In



High-chain genes	DJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged
Low-chain genes	Germ line	Germ line	Germ line	VDJ rearranged	VDJ rearranged	VDJ rearranged
Surface Ig	Absent	Absent	μ H-chain at surface as part of pre-β receptor	μ H-chain in cytoplasm and at surface	IgM expressed on cell surface	IgD and IgM made from alternatively spliced H-chain transcripts
Surface marker proteins	CD34 CD10 CD19 CD38	CD10 CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD40	CD19 CD20 CD21 CD40

FIGURE 1-6

Development stages of T and B cells. Elements of the developing T and B cell receptor for antigen are shown schematically. The classification into the various stages of B cell development is primarily defined by rearrangement of the immunoglobulin (Ig), heavy (H), and light (L) chain genes and by the absence or presence of specific surface markers. (*Adapted from CA Janeway et al [eds]: Immunobiology. The Immune Systemic Health and Disease, 4th ed. New York, Garland, 1999; with permission.*) The classification of stages of T cell development is primarily defined by cell-surface marker protein expression (sCD3, surface CD3 expression, cCD3, cytoplasmic CD3 expression; TCR, T cell receptor).

the thymus, CD34+ T cell precursors begin cytoplasmic (c) synthesis of components of the CD3 complex of TCR-associated molecules (Fig. 1-6). Within T cell precursors, TCR for antigen gene rearrangement yields two T cell lineages, expressing either TCR-αβ chains or TCR-γδ chains. T cells expressing the TCR-αβ chains constitute the majority of peripheral T cells in blood, lymph node, and spleen and terminally differentiate into either CD4+ or CD8+ cells. Cells expressing TCR-γδ chains circulate as a minor population in blood; their functions, although not fully understood, have been postulated to be those of immune surveillance at epithelial surfaces and cellular defenses against mycobacterial organisms and other intracellular bacteria through recognition of bacterial lipids.

In the thymus, the recognition of self-peptides on thymic epithelial cells, thymic macrophages, and dendritic cells plays an important role in shaping the T cell repertoire to recognize foreign antigen (*positive selection*) and in eliminating highly autoreactive T cells (*negative selection*). As immature cortical thymocytes begin to express surface TCR for antigen, autoreactive thymocytes are destroyed (negative selection), thymocytes with TCRs capable of interacting with foreign antigen peptides in the context of self-MHC antigens are activated and develop to maturity (positive selection), and thymocytes with TCRs

that are incapable of binding to self-MHC antigens die of attrition (*no selection*). Mature thymocytes that are positively selected are either CD4+ helper T cells or MHC class II–restricted cytotoxic (killer) T cells, or they are CD8+ T cells destined to become MHC class I–restricted cytotoxic T cells. *MHC class I–* or *class II–restricted* means that T cells recognize antigen peptide fragments only when they are presented in the antigen-recognition site of a class I or class II MHC molecule, respectively (Chap. 2).

After thymocyte maturation and selection, CD4 and CD8 thymocytes leave the thymus and migrate to the peripheral immune system. The thymus continues to be a contributor to the peripheral immune system, well into adult life, both normally and when the peripheral T cell pool is damaged, such as occurs in AIDS and cancer chemotherapy.

Molecular basis of T cell recognition of antigen

The TCR for antigen is a complex of molecules consisting of an antigen-binding heterodimer of either αβ or γδ chains noncovalently linked with five CD3 subunits (γ, δ, ε, ζ, and η) **(Fig. 1-7)**. The CD3 ζ chains are either disulfide-linked homodimers (CD3-ζ_2) or disulfide-linked heterodimers composed of one ζ chain and one η chain. TCR-αβ or TCR-γδ molecules must be associated with CD3 molecules to be inserted into the T cell–surface membrane, TCRα being paired with TCR-β and TCR-γ being paired with TCR-δ. Molecules of the CD3 complex mediate transduction of T cell activation signals via TCRs, while TCR-α and -β or -γ and -δ molecules combine to form the TCR antigen-binding site.

The α, β, γ, and δ TCR for antigen molecules have amino acid sequence homology and structural similarities to immunoglobulin heavy and light chains and are members of the *immunoglobulin gene superfamily* of molecules. The genes encoding TCR molecules are encoded as clusters of gene segments that rearrange during the course of T cell maturation. This creates an efficient and compact mechanism for housing the

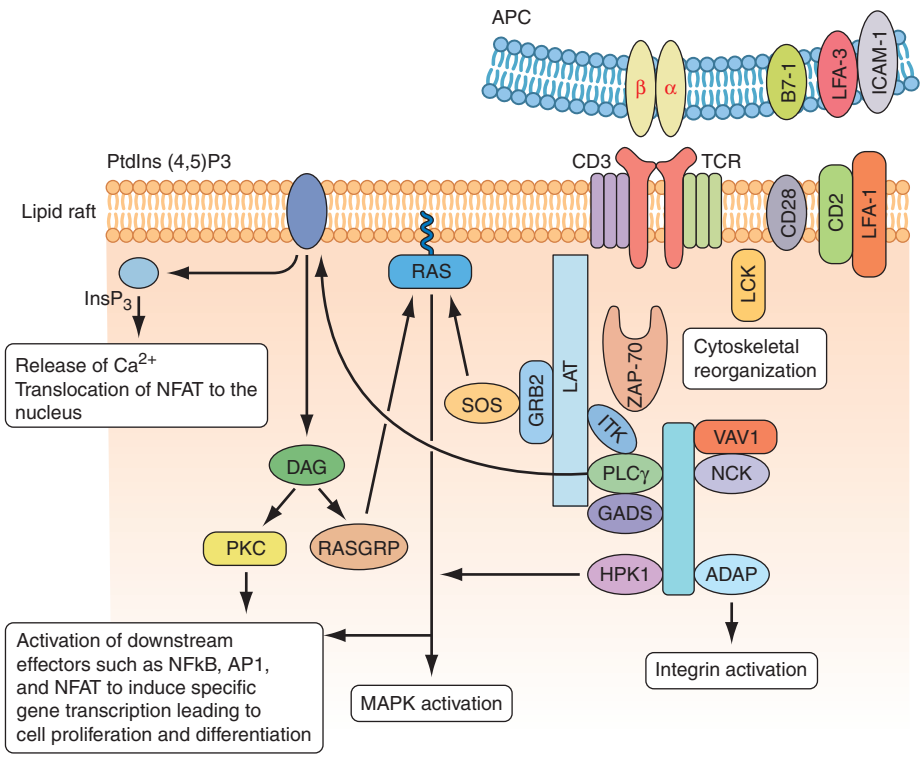


FIGURE 1-7

Signaling through the T cell receptor. Activation signals are mediated via immunoreceptor tyrosine-based activation motif (ITAM) sequences in LAT and CD3 chains (blue bars) that bind to enzymes and transduce activation signals to the nucleus via the indicated intracellular activation pathways. Ligation of the T-cell receptor (TCR) by MHC complexed with antigen results in sequential activation of LCK and γ-chain-associated protein kinase of 70 kDa (ZAP-70). ZAP-70 phosphorylates several downstream targets, including LAT (linker for activation of T cells) and SLP76 [SCR homology 2 (SH2) domain-containing leukocyte protein of 76 kDa]. SLP76 is recruited to membrane-bound LAT through its constitutive interaction with GADS (GRB2-related adaptor protein). Together, SLP76 and LAT nucleate a multimolecular signaling complex, which induces a host of downstream responses, including calcium flux, mitogen-activated protein kinase (MAPK) activation, integrin activation, and cytoskeletal reorganization. APC denotes antigen-presenting cell. (*Adapted from GA Koretzky et al: Nat Rev Immunol 6:67, 2006; with permission from Macmillan Publishers Ltd. Copyright 2006.*)

diversity requirements of antigen receptor molecules. The TCR-α chain is on chromosome 14 and consists of a series of V (variable), J (joining), and C (constant) regions. The TCR-β chain is on chromosome 7 and consists of multiple V, D (diversity), J, and C TCR-β loci. The TCR-γ chain is on chromosome 7, and the TCR-δ chain is in the middle of the TCR-α locus on chromosome 14. Thus, molecules of the TCR for antigen have constant (framework) and variable regions, and the gene segments encoding the α, β, γ, and δ chains of these molecules are recombined and selected in the thymus, culminating in synthesis of the completed molecule. In both T and B cell precursors (discussed later), DNA rearrangements of antigen receptor genes involve the same enzymes, recombinase activating gene (RAG)1 and RAG2, both DNA-dependent protein kinases.

TCR diversity is created by the different V, D, and J segments that are possible for each receptor chain by the many permutations of V, D, and J segment combinations, by "N-region diversification" due to the addition of nucleotides at the junction of rearranged gene segments, and by the pairing of individual chains to form a TCR dimer. As T cells mature in the thymus, the repertoire of antigen-reactive T cells is modified by selection processes that eliminate many autoreactive T cells, enhance the proliferation of cells that function appropriately with self-MHC molecules and antigen, and allow T cells with nonproductive TCR rearrangements to die.

TCR-αβ cells do not recognize native protein or carbohydrate antigens. Instead, T cells recognize only short (~9–13 amino acids) peptide fragments derived from protein antigens taken up or produced in APCs. Foreign antigens may be taken up by endocytosis into acidified intracellular vesicles or by phagocytosis and degraded into small peptides that associate with MHC class II molecules (exogenous antigen-presentation pathway). Other foreign antigens arise endogenously in the cytosol (such as from replicating viruses) and are broken down into small peptides that associate with MHC class I molecules (endogenous antigen-presenting pathway). Thus, APCs proteolytically degrade foreign proteins and display peptide fragments embedded in the MHC class I or II antigen-recognition site on the MHC molecule surface, where foreign peptide fragments are available to bind to TCR-αβ or TCR-γδ chains of reactive T cells. CD4 molecules act as adhesives and, by direct binding to MHC class II (DR, DQ, or DP) molecules, stabilize the interaction of TCR with peptide antigen (Fig. 1-7). Similarly, CD8 molecules also act as adhesives to stabilize the TCR-antigen interaction by direct CD8 molecule binding to MHC class I (A, B, or C) molecules.

Antigens that arise in the cytosol and are processed via the endogenous antigen-presentation pathway are cleaved into small peptides by a complex of proteases called the *proteasome*. From the proteasome, antigen peptide fragments are transported from the cytosol into the lumen of the endoplasmic reticulum by a heterodimeric complex termed *transporters associated with antigen processing*, or TAP proteins. There, MHC class I molecules in the endoplasmic reticulum membrane physically associate with processed cytosolic peptides. Following peptide association with class I molecules, peptide–class I complexes are exported to the Golgi apparatus, and then to the cell surface, for recognition by CD8+ T cells.

Antigens taken up from the extracellular space via endocytosis into intracellular acidified vesicles are degraded by vesicle proteases into peptide fragments. Intracellular vesicles containing MHC class II molecules fuse with peptide-containing vesicles, thus allowing peptide fragments to physically bind to MHC class II molecules. Peptide–MHC class II complexes are then transported to the cell surface for recognition by CD4+ T cells (Chap. 2).

Whereas it is generally agreed that the TCR-αβ receptor recognizes peptide antigens in the context of MHC class I or class II molecules, lipids in the cell wall of intracellular bacteria such as *M. tuberculosis* can also be presented to a wide variety of T cells, including subsets of TCR-γδ T cells, and a subset of CD8+ TCR-αβ T cells. Importantly, bacterial lipid antigens are not presented in the context of MHC class I or II molecules, but rather are presented in the context of MHC-related CD1 molecules. Some γδ T cells that recognize lipid antigens via CD1 molecules have very restricted TCR usage, do not need antigen priming to respond to bacterial lipids, and may actually be a form of innate rather than acquired immunity to intracellular bacteria.

Just as foreign antigens are degraded and their peptide fragments presented in the context of MHC class I or class II molecules on APCs, endogenous self-proteins also are degraded and self-peptide fragments are presented to T cells in the context of MHC class I or class II molecules on APCs. In peripheral lymphoid organs, there are T cells that are capable of recognizing self-protein fragments but normally are *anergic* or *tolerant*, i.e., nonresponsive to self-antigenic stimulation, due to lack of self-antigen upregulating APC *co-stimulatory molecules* such as B7-1 (CD80) and B7-2 (CD86) (discussed later).

Once engagement of mature T cell TCR by foreign peptide occurs in the context of self–MHC class I or class II molecules, binding of non-antigen-specific adhesion ligand pairs such as CD54-CD11/CD18 and CD58-CD2 stabilizes MHC peptide–TCR binding, and the expression of these adhesion molecules is upregulated (Fig. 1-7). Once antigen ligation of the TCR occurs, the T cell membrane is partitioned into *lipid membrane microdomains*, or *lipid rafts*, that coalesce the key signaling molecules TCR/CD3 complex, CD28, CD2, LAT (linker for activation of T cells), intracellular

activated (dephosphorylated) src family protein tyrosine kinases (PTKs), and the key CD3ζ-associated protein-70 (ZAP-70) PTK (Fig. 1-7). Importantly, during T cell activation, the CD45 molecule, with protein tyrosine phosphatase activity is partitioned away from the TCR complex to allow activating phosphorylation events to occur. The coalescence of signaling molecules of activated T lymphocytes in *microdomains* has suggested that T cell–APC interactions can be considered *immunologic synapses*, analogous in function to neuronal synapses.

After TCR-MHC binding is stabilized, activation signals are transmitted through the cell to the nucleus and lead to the expression of gene products important in mediating the wide diversity of T cell functions such as the secretion of IL-2. The TCR does not have intrinsic signaling activity but is linked to a variety of signaling pathways via immunoreceptor tyrosine-based activation motifs (ITAMs) expressed on the various CD3 chains that bind to proteins that mediate signal transduction. Each of the pathways results in the activation of particular transcription factors that control the expression of cytokine and cytokine receptor genes. Thus, antigen-MHC binding to the TCR induces the activation of the src family of PTKs, fyn and lck (lck is associated with CD4 or CD8 co-stimulatory molecules); phosphorylation of CD3ζ chain; activation of the related tyrosine kinases ZAP-70 and syk; and downstream activation of the calcium-dependent calcineurin pathway, the ras pathway, and the protein kinase C pathway. Each of these pathways leads to activation of specific families of transcription factors (including NF-AT, fos and jun, and rel/NF-κB) that form heteromultimers capable of inducing expression of IL-2, IL-2 receptor, IL-4, TNF-α, and other T cell mediators.

In addition to the signals delivered to the T cell from the TCR complex and CD4 and CD8, molecules on the T cell such as CD28 and inducible co-stimulator (ICOS) and molecules on dendritic cells such as B7-1 (CD80) and B7-2 (CD86) also deliver important co-stimulatory signals that upregulate T cell cytokine production and are essential for T cell activation. If signaling through CD28 or ICOS does not occur, or if CD28 is blocked, the T cell becomes anergic rather than activated (see "Immune Tolerance and Autoimmunity").

T cell superantigens

Conventional antigens bind to MHC class I or II molecules in the groove of the αβ heterodimer and bind to T cells via the V regions of the TCR-α and -β chains. In contrast, superantigens bind directly to the lateral portion of the TCR-β chain and MHC class II β chain and stimulate T cells based solely on the Vβ gene segment utilized independent of the D, J, and Vα sequences present. *Superantigens* are protein molecules capable of activating up to 20% of the peripheral T cell pool, whereas conventional antigens activate <1 in 10,000 T cells. T cell superantigens include staphylococcal enterotoxins and other bacterial products. Superantigen stimulation of human peripheral T cells occurs in the clinical setting of *staphylococcal toxic shock syndrome*, leading to massive overproduction of T cell cytokines that leads to hypotension and shock.

B cells

Mature B cells constitute 10–15% of human peripheral blood lymphocytes, 20–30% of lymph node cells, 50% of splenic lymphocytes, and ~10% of bone marrow lymphocytes. B cells express on their surface intramembrane immunoglobulin (Ig) molecules that function as B cell receptors (BCRs) for antigen in a complex of Ig-associated α and β signaling molecules with properties similar to those described in T cells **(Fig. 1-8)**. Unlike T cells, which recognize only processed peptide fragments of conventional antigens embedded in the notches of MHC class I and class II antigens of APCs, B cells are capable of recognizing and proliferating to whole unprocessed native antigens via antigen binding to B cell–surface Ig (sIg) receptors. B cells also express surface receptors for the Fc region of IgG molecules (CD32) as well as receptors for activated complement components (C3d or CD21, C3b or CD35). The primary function of B cells is to produce antibodies. B cells also serve as APCs and are highly efficient at antigen processing. Their antigen-presenting function is enhanced by a variety of cytokines. Mature B cells are derived from bone marrow precursor cells that arise continuously throughout life (Fig. 1-6).

B lymphocyte development can be separated into antigen-independent and antigen-dependent phases. Antigen-independent B cell development occurs in primary lymphoid organs and includes all stages of B cell maturation up to the sIg+ mature B cell. Antigen-dependent B cell maturation is driven by the interaction of antigen with the mature B cell sIg, leading to memory B cell induction, Ig class switching, and plasma cell formation. Antigen-dependent stages of B cell maturation occur in secondary lymphoid organs, including lymph node, spleen, and gut Peyer's patches. In contrast to the T cell repertoire that is generated intrathymically before contact with foreign antigen, the repertoire of B cells expressing diverse antigen-reactive sites is modified by further alteration of Ig genes after stimulation by antigen—a process called *somatic hypermutation*—which occurs in lymph node germinal centers.

During B cell development, diversity of the antigen-binding variable region of Ig is generated by an ordered set of Ig gene rearrangements that are similar to the rearrangements undergone by TCR α, β, γ, and δ genes. For the heavy chain, there is first a rearrangement of D segments to J segments, followed by

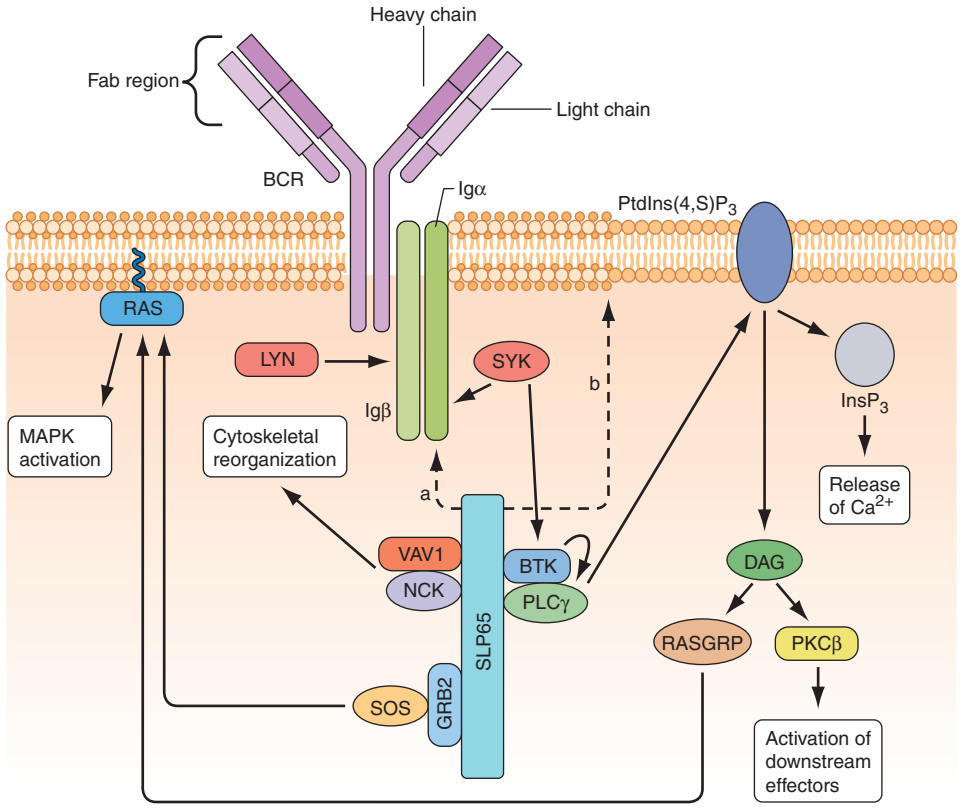


FIGURE 1-8

B cell receptor (BCR) activation results in the sequential activation of protein tyrosine kinases, which results in the formation of a signaling complex and activation of downstream pathways as shown. Whereas SLP76 is recruited to the membrane through GADS and LAT, the mechanism of SLP65 recruitment is unclear. Studies have indicated two mechanisms: (a) direct binding by the SH2 domain of SLP65 to immunoglobulin (Ig) of the BCR complex or (b) membrane recruitment through a leucine zipper in the amino terminus of SLP65 and an unknown binding partner. ADAP, adhesion- and degranulation-promoting adaptor protein; AP1, activator protein 1; BTK, Bruton's tyrosine kinase; DAG, diacylglycerol; GRB2, growth factor receptor–bound protein 2; HPK1, hematopoietic progenitor kinase 1; $InsP_3$, inositol-1,4,5-trisphosphate; ITK, interleukin-2-inducible T cell kinase; NCK, noncatalytic region of tyrosine kinase; NF-B, nuclear factor B; PKC, protein kinase C; PLC, phospholipase C; $PtdIns(4,5)P_2$, phosphatidylinositol-4, 5-bisphosphate; RASGRP, RAS guanyl-releasing protein; SOS, son of sevenless homologue; SYK, spleen tyrosine kinase. (*Adapted from GA Koretzky et al: Nat Rev Immunol 6:67, 2006; with permission from Macmillan Publishers Ltd. Copyright 2006.*)

a second rearrangement between a V gene segment and the newly formed D-J sequence; the C segment is aligned to the V-D-J complex to yield a functional Ig heavy chain gene (V-D-J-C). During later stages, a functional κ or γ light chain gene is generated by rearrangement of a V segment to a J segment, ultimately yielding an intact Ig molecule composed of heavy and light chains.

The process of Ig gene rearrangement is regulated and results in a single antibody specificity produced by each B cell, with each Ig molecule comprising one type of heavy chain and one type of light chain. Although each B cell contains two copies of Ig light and heavy chain genes, only one gene of each type is productively rearranged and expressed in each B cell, a process termed *allelic exclusion*.

There are ~300 $V_κ$ genes and 5 $J_κ$ genes, resulting in the pairing of $V_κ$ and $J_κ$ genes to create >1500 different light chain combinations. The number of distinct κ light chains that can be generated is increased by somatic mutations within the $V_κ$ and $J_κ$ genes, thus creating large numbers of possible specificities from a limited amount of germ-line genetic information. As noted earlier, in heavy chain Ig gene rearrangement, the VH domain is created by the joining of three types of germ-line genes called V_H, D_H, and J_H, thus allowing for even greater diversity in the variable region of heavy chains than of light chains.

The most immature B cell precursors (early pro-B cells) lack cytoplasmic Ig (cIg) and sIg (Fig. 1-6). The large pre-B cell is marked by the acquisition of the surface pre-BCR composed of μ heavy (H) chains and a pre-B light chain, termed ψLC. ψLC is a surrogate light chain receptor encoded by the nonrearranged V pre-B and the γ5 light chain locus (the pre-BCR). Pro- and pre-B cells are driven to proliferate and mature by

signals from bone marrow stroma—in particular, IL-7. Light chain rearrangement occurs in the small pre-B cell stage such that the full BCR is expressed at the immature B cell stage. Immature B cells have rearranged Ig light chain genes and express sIgM. As immature B cells develop into mature B cells, sIgD is expressed as well as sIgM. At this point, B lineage development in bone marrow is complete, and B cells exit into the peripheral circulation and migrate to secondary lymphoid organs to encounter specific antigens.

Random rearrangements of Ig genes occasionally generate self-reactive antibodies, and mechanisms must be in place to correct these mistakes. One such mechanism is BCR editing, whereby autoreactive BCRs are mutated to not react with self-antigens. If receptor editing is unsuccessful in eliminating autoreactive B cells, then autoreactive B cells undergo negative selection in the bone marrow through induction of apoptosis after BCR engagement of self-antigen.

After leaving the bone marrow, B cells populate peripheral B cell sites, such as lymph node and spleen, and await contact with foreign antigens that react with each B cell's clonotypic receptor. Antigen-driven B cell activation occurs through the BCR, and a process known as *somatic hypermutation* takes place whereby point mutations in rearranged H- and L-genes give rise to mutant sIg molecules, some of which bind antigen better than the original sIg molecules. Somatic hypermutation, therefore, is a process whereby memory B cells in peripheral lymph organs have the best binding, or the highest-affinity antibodies. This overall process of generating the best antibodies is called *affinity maturation of antibody*.

Lymphocytes that synthesize IgG, IgA, and IgE are derived from sIgM+, sIgD+ mature B cells. Ig class switching occurs in lymph node and other peripheral lymphoid tissue germinal centers. CD40 on B cells and CD40 ligand on T cells constitute a critical co-stimulatory receptor-ligand pair of immune-stimulatory molecules. Pairs of CD40+ B cells and CD40 ligand+ T cells bind and drive B cell Ig class switching via T cell–produced cytokines such as IL-4 and TGF-β. IL-1, -2, -4, -5, and -6 synergize to drive mature B cells to proliferate and differentiate into Ig-secreting cells.

Humoral mediators of adaptive immunity: immunoglobulins

Immunoglobulins are the products of differentiated B cells and mediate the humoral arm of the immune response. The primary functions of antibodies are to bind specifically to antigen and bring about the inactivation or removal of the offending toxin, microbe, parasite, or other foreign substance from the body. The structural basis of Ig molecule function and Ig gene organization has provided insight into the role of antibodies in normal protective immunity, pathologic immune-mediated damage by immune complexes, and autoantibody formation against host determinants.

All immunoglobulins have the basic structure of two heavy and two light chains (Fig. 1-8). Immunoglobulin isotype (i.e., G, M, A, D, E) is determined by the type of Ig heavy chain present. IgG and IgA isotypes can be divided further into subclasses (G1, G2, G3, G4, and A1, A2) based on specific antigenic determinants on Ig heavy chains. The characteristics of human immunoglobulins are outlined in **Table 1-13**. The four chains are covalently linked by disulfide bonds. Each chain is made up of a V region and C regions (also called *domains*), themselves made up of units of ~110 amino acids. Light chains have one variable (V_L) and one constant (C_L) unit; heavy chains have one variable unit (V_H) and three or four constant (C_H) units, depending on isotype. As the name suggests, the constant, or C, regions of Ig molecules are made up of homologous sequences and share the same primary structure as all other Ig chains of the same isotype and subclass. Constant regions are involved in biologic functions of Ig molecules. The C_H2 domain of IgG and the C_H4 units of IgM are involved with the binding of the C1q portion of C1 during complement activation. The C_H region at the carboxy-terminal end of the IgG molecule, the Fc region, binds to surface Fc receptors (CD16, CD32, CD64) of macrophages, dendritic cells, NK cells, B cells, neutrophils, and eosinophils.

Variable regions (V_L and V_H) constitute the antibody-binding (Fab) region of the molecule. Within the V_L and V_H regions are hypervariable regions (extreme sequence variability) that constitute the antigen-binding site unique to each Ig molecule. The idiotype is defined as the specific region of the Fab portion of the Ig molecule to which antigen binds. Antibodies against the idiotype portion of an antibody molecule are called *anti-idiotype antibodies*. The formation of such antibodies in vivo during a normal B cell antibody response may generate a negative (or "off") signal to B cells to terminate antibody production.

IgG constitutes ~75–85% of total serum immunoglobulin. The four IgG subclasses are numbered in order of their level in serum, IgG1 being found in greatest amounts and IgG4 the least. IgG subclasses have clinical relevance in their varying ability to bind macrophage and neutrophil Fc receptors and to activate complement (Table 1-13). Moreover, selective deficiencies of certain IgG subclasses give rise to clinical syndromes in which the patient is inordinately susceptible to bacterial infections. IgG antibodies are frequently the predominant antibody made after rechallenge of the host with antigen (secondary antibody response).

IgM antibodies normally circulate as a 950-kDa pentamer with 160-kDa bivalent monomers joined by a molecule called the *J chain*, a 15-kDa nonimmunoglobulin

TABLE 1-13

PHYSICAL, CHEMICAL, AND BIOLOGIC PROPERTIES OF HUMAN IMMUNOGLOBULINS

PROPERTY	IgG	IgA	IgM	IgD	IgE
Usual molecular form	Monomer	Monomer, dimer	Pentamer, hexamer	Monomer	Monomer
Other chains	None	J chain, SC	J chain	None	None
Subclasses	G1, G2, G3, G4	A1, A2	None	None	None
Heavy chain allotypes	Gm (=30)	No A1, A2m (2)	None	None	None
Molecular mass, kDa	150	160, 400	950, 1150	175	190
Serum level in average adult, mg/mL	9.5–12.5	1.5–2.6	0.7–1.7	0.04	0.0003
Percentage of total serum Ig	75–85	7–15	5–10	0.3	0.019
Serum half-life, days	23	6	5	3	2.5
Synthesis rate, mg/kg per day	33	65	7	0.4	0.016
Antibody valence	2	2, 4	10, 12	2	2
Classical complement activation	+(G1, 2?, 3)	–	++	–	–
Alternate complement activation	+(G4)	+	–	+	–
Binding cells via Fc	Macrophages, neutrophils, large granular lymphocytes	Lymphocytes	Lymphocytes	None	Mast cells, basophils, B cells
Biologic properties	Placental transfer, secondary Ab for most antipathogen responses	Secretory immunoglobulin	Primary Ab responses	Marker for mature B cells	Allergy, antiparasite responses

Source: After L Carayannopoulos, JD Capra, in WE Paul (ed): *Fundamental Immunology*, 3rd ed. New York, Raven, 1993; with permission.

molecule that also effects polymerization of IgA molecules. IgM is the first immunoglobulin to appear in the immune response (primary antibody response) and is the initial type of antibody made by neonates. Membrane IgM in the monomeric form also functions as a major antigen receptor on the surface of mature B cells (Fig. 1-13). IgM is an important component of immune complexes in autoimmune diseases. For example, IgM antibodies against IgG molecules (rheumatoid factors) are present in high titers in *rheumatoid arthritis*, other collagen diseases, and some infectious diseases (*subacute bacterial endocarditis*).

IgA constitutes only 7–15% of total serum immunoglobulin but is the predominant class of immunoglobulin in secretions. IgA in secretions (tears, saliva, nasal secretions, gastrointestinal tract fluid, and human milk) is in the form of secretory IgA (sIgA), a polymer consisting of two IgA monomers, a joining molecule, again called the J chain, and a glycoprotein called the *secretory protein*. Of the two IgA subclasses, IgA1 is primarily found in serum, whereas IgA2 is more prevalent in secretions. IgA fixes complement via the alternative complement pathway and has potent antiviral activity in humans by prevention of virus binding to respiratory and gastrointestinal epithelial cells.

IgD is found in minute quantities in serum and, together with IgM, is a major receptor for antigen on the B cell surface. IgE, which is present in serum in very low concentrations, is the major class of immunoglobulin involved in arming mast cells and basophils by binding to these cells via the Fc region. Antigen cross-linking of IgE molecules on basophil and mast cell surfaces results in release of mediators of the immediate hypersensitivity (allergic) response (Table 1-13).

CELLULAR INTERACTIONS IN REGULATION OF NORMAL IMMUNE RESPONSES

The net result of activation of the humoral (B cell) and cellular (T cell) arms of the adaptive immune system by foreign antigen is the elimination of antigen directly by specific effector T cells or in concert with specific antibody. Figure 1-2 is a simplified schematic diagram of the T and B cell responses indicating some of these cellular interactions.

The expression of adaptive immune cell function is the result of a complex series of immunoregulatory events that occur in phases. Both T and B lymphocytes mediate immune functions, and each of these cell types, when given appropriate signals, passes through stages, from activation and induction through proliferation, differentiation, and ultimately effector functions. The effector function expressed may be at the end point of a response, such as secretion of antibody by a differentiated plasma cell, or it might serve a regulatory function that modulates other functions, such as is seen with CD4+ and CD8+ T lymphocytes that modulate both differentiation of B cells and activation of CD8+ cytotoxic T cells.

CD4 helper T cells can be subdivided on the basis of cytokines produced (Fig. 1-2). Activated T_H1-type helper T cells secrete IL-2, IFN-γ, IL-3, TNF-α, GM-CSF, and TNF-β, while activated T_H2-type helper T cells secrete IL-3, -4, -5, -6, -10, and -13. T_H1 CD4+ T cells, through elaboration of IFN-γ, have a central role in mediating intracellular killing by a variety of pathogens. T_H1 CD4+ T cells also provide T cell help for generation of cytotoxic T cells and some types of opsonizing antibody, and they generally respond to antigens that lead to delayed hypersensitivity types of immune responses for many intracellular viruses and bacteria (such as HIV or *M. tuberculosis*). In contrast, T_H2 cells have a primary role in regulatory humoral immunity and isotype switching. T_H2 cells, through production of IL-4 and IL-10, have a regulatory role in limiting proinflammatory responses mediated by T_H1 cells (Fig. 1-2). In addition, T_H2 CD4+ T cells provide help to B cells for specific Ig production and respond to antigens that require high antibody levels for foreign antigen elimination (extracellular encapsulated bacteria such as *Streptococcus pneumoniae* and certain parasite infections). More recently, a new subset of the T_H family has been described termed T_H17 characterized by these cells to secrete cytokines such as IL-17, -22, and -26. T_H17 cells have been shown to play a role in autoimmune inflammatory disorders in addition to defense against extracellular bacteria and fungi, particularly at mucosal surfaces (Fig. 1-3). In summary, the type of T cell response generated in an immune response is determined by the microbe PAMPs presented to the DCs, the TLRs on the DCs that become activated, the types of DCs that are activated, and the cytokines that are produced (Table 1-4). Commonly, myeloid DCs produce IL-12 and activate T_H1 T cell responses that result in IFN-γ and cytotoxic T cell induction, and plasmacytoid DCs produce IFN-α and lead to T_H2 responses that result in IL-4 production and enhanced antibody responses.

As shown in Figs. 1-2 and 1-3, upon activation by DCs, T cell subsets that produce IL-2, IL-3, IFN-γ, and/or IL-4, -5, -6, -10, and -13 are generated and exert positive and negative influences on effector T and B cells. For B cells, trophic effects are mediated by a variety of cytokines, particularly T cell–derived IL-3, -4, -5, and -6, that act at sequential stages of B cell maturation, resulting in B cell proliferation, differentiation, and ultimately antibody secretion. For cytotoxic T cells, trophic factors include inducer T cell secretion of IL-2, IFN-γ, and IL-12.

An important type of immunomodulatory T cell that controls immune responses is *CD4+ and CD8+ T regulatory cells*. These cells constitutively express the α chain of the IL-2 receptor (CD25), produce large amounts of IL-10, and can suppress both T and B cell responses. T regulatory cells are induced by immature dendritic cells and play key roles in maintaining tolerance to self-antigens in the periphery. Loss of T regulatory cells is the cause of organ-specific autoimmune disease in mice such as autoimmune thyroiditis, adrenalitis, and oophoritis (see "Immune Tolerance and Autoimmunity"). T regulatory cells also play key roles in controlling the magnitude and duration of immune responses to microbes. Normally, after the initial immune response to a microbe has eliminated the invader, T regulatory cells are activated to suppress the antimicrobe response and prevent host injury. Some microbes have adapted to induce T regulatory cell activation at the site of infection to promote parasite infection and survival. In *Leishmania* infection, the parasite locally induces T regulatory cell accumulation at skin infection sites that dampens anti-*Leishmania* T cell responses and prevents elimination of the parasite. It is thought that many chronic infections such as by *M. tuberculosis* are associated with abnormal T regulatory cell activation that prevents elimination of the microbe.

Although B cells recognize native antigen via B cell–surface Ig receptors, B cells require T cell help to produce high-affinity antibody of multiple isotypes that are the most effective in eliminating foreign antigen. This T cell dependence likely functions in the regulation of B cell responses and in protection against excessive autoantibody production. T cell–B cell interactions that lead to high-affinity antibody production require (1) processing of native antigen by B cells and expression of peptide fragments on the B cell surface for presentation to T_H cells, (2) the ligation of B cells by both the TCR complex and the CD40 ligand, (3) induction of the process termed *antibody isotype switching* in antigen-specific B cell clones, and (4) induction of the process of affinity maturation of antibody in the germinal centers of B cell follicles of lymph node and spleen.

Naïve B cells express cell-surface IgD and IgM, and initial contact of naïve B cells with antigen is via binding of native antigen to B cell–surface IgM. T cell cytokines, released following T_H2 cell contact with B cells

or by a "bystander" effect, induce changes in Ig gene conformation that promote recombination of Ig genes. These events then result in the "switching" of expression of heavy chain exons in a triggered B cell, leading to the secretion of IgG, IgA, or, in some cases, IgE antibody with the same V region antigen specificity as the original IgM antibody, for response to a wide variety of extracellular bacteria, protozoa, and helminths. CD40 ligand expression by activated T cells is critical for induction of B cell antibody isotype switching and for B cell responsiveness to cytokines. Patients with mutations in T cell CD40 ligand have B cells that are unable to undergo isotype switching, resulting in lack of memory B cell generation and the immunodeficiency syndrome of *X-linked hyper-IgM syndrome*.

IMMUNE TOLERANCE AND AUTOIMMUNITY

Immune tolerance is defined as the absence of activation of pathogenic autoreactivity. *Autoimmune diseases* are syndromes caused by the activation of T or B cells or both, with no evidence of other causes such as infections or malignancies (Chap. 3). Once thought to be mutually exclusive, immune tolerance and autoimmunity are now both recognized to be present normally in health; when abnormal, they represent extremes from the normal state. For example, it is now known that low levels of autoreactivity of T and B cells with self-antigens in the periphery are critical to their survival. Similarly, low levels of autoreactivity and thymocyte recognition of self-antigens in the thymus are the mechanisms whereby (1) normal T cells are positively selected to survive and leave the thymus to respond to foreign microbes in the periphery and (2) T cells highly reactive to self-antigens are negatively selected and die to prevent overly self-reactive T cells from getting into the periphery (central tolerance). However, not all self-antigens are expressed in the thymus to delete highly self-reactive T cells, and there are mechanisms for peripheral tolerance induction of T cells as well. Unlike the presentation of microbial antigens by mature dendritic cells, the presentation of self-antigens by immature dendritic cells neither activates nor matures the dendritic cells to express high levels of co-stimulatory molecules such as B7-1 (CD80) or B7-2 (CD86). When peripheral T cells are stimulated by dendritic cells expressing self-antigens in the context of HLA molecules, sufficient stimulation of T cells occurs to keep them alive, but otherwise they remain anergic, or nonresponsive, until they contact a dendritic cell with high levels of co-stimulatory molecules expressing microbial antigens. In the latter setting, normal T cells then become activated to respond to the microbe. If B cells have high-self-reactivity BCRs, they normally undergo either deletion in the bone marrow or receptor editing to express a less autoreactive receptor. Although many autoimmune diseases are characterized by abnormal or pathogenic autoantibody production **(Table 1-14)**, most autoimmune diseases are caused by a combination of excess T and B cell reactivity.

Multiple factors contribute to the genesis of clinical autoimmune disease syndromes, including genetic susceptibility (Table 1-14), environmental immune stimulants such as drugs [e.g., procainamide and phenytoin (Dilantin) with drug-induced systemic lupus erythematosus], infectious agent triggers (such as Epstein-Barr virus and autoantibody production against red blood cells and platelets), and loss of T regulatory cells (leading to thyroiditis, adrenalitis, and oophoritis).

Immunity at mucosal surfaces

Mucosa covering the respiratory, digestive, and urogenital tracts; the eye conjunctiva; the inner ear; and the ducts of all exocrine glands contain cells of the innate and adaptive mucosal immune system that protect these surfaces against pathogens. In the healthy adult, mucosa-associated lymphoid tissue (MALT) contains 80% of all immune cells within the body and constitutes the largest mammalian lymphoid organ system.

MALT has three main functions: (1) to protect the mucous membranes from invasive pathogens; (2) to prevent uptake of foreign antigens from food, commensal organisms, and airborne pathogens and particulate matter; and (3) to prevent pathologic immune responses from foreign antigens if they do cross the mucosal barriers of the body **(Fig. 1-9)**.

MALT is a compartmentalized system of immune cells that functions independently from systemic immune organs. Whereas the systemic immune organs are essentially sterile under normal conditions and respond vigorously to pathogens, MALT immune cells are continuously bathed in foreign proteins and commensal bacteria, and they must select those pathogenic antigens that must be eliminated. MALT contains anatomically defined foci of immune cells in the intestine, tonsil, appendix, and peribronchial areas that are inductive sites for mucosal immune responses. From these sites, immune T and B cells migrate to effector sites in mucosal parenchyma and exocrine glands where mucosal immune cells eliminate pathogen-infected cells. In addition to mucosal immune responses, all mucosal sites have strong mechanical and chemical barriers and cleansing functions to repel pathogens.

Key components of MALT include specialized epithelial cells called "membrane" or "M" cells that take up antigens and deliver them to dendritic cells or other APCs. Effector cells in MALT include B cells producing antipathogen neutralizing antibodies of secretory IgA as well as IgG isotype, T cells producing similar cytokines

TABLE 1-14

RECOMBINANT OR PURIFIED AUTOANTIGENS RECOGNIZED BY AUTOANTIBODIES ASSOCIATED WITH HUMAN AUTOIMMUNE DISORDERS

AUTOANTIGEN	AUTOIMMUNE DISEASES	AUTOANTIGEN	AUTOIMMUNE DISEASES
Cell- or Organ-Specific Autoimmunity			
Acetylcholine receptor	Myasthenia gravis	Insulin receptor	Type B insulin resistance, acanthosis, systemic lupus erythematosus (SLE)
Actin	Chronic active hepatitis, primary biliary cirrhosis	Intrinsic factor type 1	Pernicious anemia
Adenine nucleotide translator (ANT)	Dilated cardiomyopathy, myocarditis	Leukocyte function-associated antigen (LFA-1)	Treatment-resistant Lyme arthritis
β-Adrenoreceptor	Dilated cardiomyopathy		
Aromatic L-amino acid decarboxylase	Autoimmune polyendocrine syndrome type 1 (APS-1)	Myelin-associated glycoprotein (MAG)	Polyneuropathy
Asialoglycoprotein receptor	Autoimmune hepatitis	Myelin-basic protein	Multiple sclerosis, demyelinating diseases
Bactericidal/permeability-increasing protein (Bpi)	Cystic fibrosis vasculitides	Myelin oligodendrocyte glycoprotein (MOG)	Multiple sclerosis
Calcium-sensing receptor	Acquired hypoparathyroidism	Myosin	Rheumatic fever
Cholesterol side-chain cleavage enzyme (CYPIIa)	Autoimmune polyglandular syndrome-1	p-80-Collin	Atopic dermatitis
Collagen type IV-α3-chain	Goodpasture syndrome	Pyruvate dehydrogenase complex-E2 (PDC-E2)	Primary biliary cirrhosis
Cytochrome P450 2D6 (CYP2D6)	Autoimmune hepatitis		
Desmin	Crohn's disease, coronary artery disease	Sodium iodide symporter (NIS)	Graves' disease, autoimmune hypothyroidism
Desmoglein 1	Pemphigus foliaceus		
Desmoglein 3	Pemphigus vulgaris	SOX-10	Vitiligo
F-actin	Autoimmune hepatitis	Thyroid and eye muscle shared protein	Thyroid-associated ophthalmopathy
GM gangliosides	Guillain-Barré syndrome		
Glutamate decarboxylase (GAD65)	Type 1 diabetes, stiff-person syndrome	Thyroglobulin	Autoimmune thyroiditis
Glutamate receptor (GLUR)	Rasmussen encephalitis	Thyroid peroxidase	Autoimmune Hashimoto thyroiditis
H/K ATPase	Autoimmune gastritis	Thyrotropin receptor	Graves' disease
17-α-Hydroxylase (CYP17)	Autoimmune polyglandular syndrome-1	Tissue transglutaminase	Celiac disease
21-Hydroxylase (CYP21)	Addison disease	Transcription coactivator p75	Atopic dermatitis
IA-2 (ICA512)	Type 1 diabetes	Tryptophan hydroxylase	Autoimmune polyglandular syndrome-1
Insulin	Type 1 diabetes, insulin hypoglycemic syndrome (Hirata disease)	Tyrosinase Tyrosine hydroxylase	Vitiligo, metastatic melanoma Autoimmune polyglandular syndrome-1
Systemic Autoimmunity			
ACTH	ACTH deficiency	Histone H2A-H2B-DNA	SLE
Aminoacyl-tRAN histidyl synthetase	Myositis, dermatomyositis	IgE receptor	Chronic idiopathic urticaria

(*continued*)

TABLE 1-14

RECOMBINANT OR PURIFIED AUTOANTIGENS RECOGNIZED BY AUTOANTIBODIES ASSOCIATED WITH HUMAN AUTOIMMUNE DISORDERS (*CONTINUED*)

AUTOANTIGEN	AUTOIMMUNE DISEASES	AUTOANTIGEN	AUTOIMMUNE DISEASES
Systemic Autoimmunity			
Aminoacyl-tRNA synthetase (several)	Polymyositis, dermatomyositis	Keratin	RA
Cardiolipin	SLE, anti-phospholipid syndrome	Ku-DNA-protein kinase	SLE
Carbonic anhydrase II	SLE, Sjögren's syndrome, systemic sclerosis	Ku-nucleoprotein La phosphoprotein (La 55-B)	Connective tissue syndrome Sjögren's syndrome
Collagen (multiple types)	Rheumatoid arthritis (RA), SLE, progressive systemic sclerosis	Myeloperoxidase	Necrotizing and crescentic glomerulonephritis (NCGN), systemic vasculitis
Centromere-associated proteins	Systemic sclerosis	Proteinase 3 (PR3)	Granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
DNA-dependent nucleoside-stimulated ATPase	Dermatomyositis	RNA polymerase I–III (RNP)	Systemic sclerosis, SLE
Fibrillarin	Scleroderma	Signal recognition protein (SRP54)	Polymyositis
Fibronectin	SLE, RA, morphea	Topoisomerase-1 (Scl-70)	Scleroderma, Raynaud syndrome
Glucose-6-phosphate isomerase	RA	Tublin	Chronic liver disease, visceral leishmaniasis
β2-Glycoprotein I (B2-GPI)	Primary antiphospholipid syndrome		
Golgin (95, 97, 160, 180) Heat shock protein	Sjögren's syndrome, SLE, RA Various immune-related disorders	Vimentin	Systemic autoimmune disease
Hemidesmosomal protein 180	Bullous pemphigoid, herpes gestationis, cicatricial pemphigoid		
Plasma Protein and Cytokine Autoimmunity			
C1 inhibitor	Autoimmune C1 deficiency	Glycoprotein IIb/IIIg and Ib/IX	Autoimmune thrombocytopenia purpura
C1q	SLE, membrane proliferative glomerulonephritis (MPGN)	IgA	Immunodeficiency associated with SLE, pernicious anemia, thyroiditis, Sjögren's syndrome and chronic active hepatitis
Cytokines (IL-1α, IL-1β, IL-6, IL-10, LIF)	RA, systemic sclerosis, normal subjects		
Factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, thrombin vWF	Prolonged coagulation time	Oxidized LDL (OxLDL)	Atherosclerosis
Cancer and Paraneoplastic Autoimmunity			
Amphiphysin	Neuropathy, small cell lung cancer	p62 (IGF-II mRNA-binding protein)	Hepatocellular carcinoma (China)
Cyclin B1	Hepatocellular carcinoma	Recoverin	Cancer-associated retinopathy
DNA topoisomerase II	Liver cancer	Ri protein	Paraneoplastic opsoclonus myoclonus ataxia
Desmoplakin	Paraneoplastic pemphigus		

(*continued*)

TABLE 1-14

RECOMBINANT OR PURIFIED AUTOANTIGENS RECOGNIZED BY AUTOANTIBODIES ASSOCIATED WITH HUMAN AUTOIMMUNE DISORDERS (*CONTINUED*)

AUTOANTIGEN	AUTOIMMUNE DISEASES	AUTOANTIGEN	AUTOIMMUNE DISEASES
Cancer and Paraneoplastic Autoimmunity			
Gephyrin	Paraneoplastic stiff-person syndrome	βIV spectrin	Lower motor neuron syndrome
Hu proteins	Paraneoplastic encephalomyelitis	Synaptotagmin	Lambert-Eaton myasthenic syndrome
Neuronal nicotinic acetylcholine receptor	Subacute autonomic neuropathy, cancer	Voltage-gated calcium channels	Lambert-Eaton myasthenic syndrome
p53	Cancer, SLE	Yo protein	Paraneoplastic cerebellar degeneration

Source: From A Lernmark et al: J Clin Invest 108:1091, 2001; with permission.

as in systemic immune system response, and T helper and cytotoxic T cells that respond to pathogen-infected cells.

Secretory IgA is produced in amounts of >50 mg/kg of body weight per 24 h and functions to inhibit bacterial adhesion, inhibit macromolecule absorption in the gut, neutralize viruses, and enhance antigen elimination in tissue through binding to IgA and receptor-mediated transport of immune complexes through epithelial cells.

Recent studies have demonstrated the importance of commensal gut and other mucosal bacteria to the health of the human immune system. Normal commensal flora induces anti-inflammatory events in the gut and protects epithelial cells from pathogens through TLRs and other PRR signaling. When the gut is depleted of normal commensal flora, the immune system becomes abnormal, with loss of T_H1 T cell function. Restoration of the normal gut flora can reestablish the balance in T helper cell ratios characteristic of the normal immune system. When the gut barrier is intact, either antigens do not transverse the gut epithelium or, when pathogens are present, a self-limited, protective MALT immune response eliminates the pathogen **(Fig. 1-9)**. However, when the gut barrier breaks down, immune responses to commensal flora antigens can cause inflammatory bowel diseases such as *Crohn's disease* and, perhaps, *ulcerative colitis* (Fig. 1-9). Uncontrolled MALT immune responses to food antigens, such as gluten, can cause *celiac disease*.

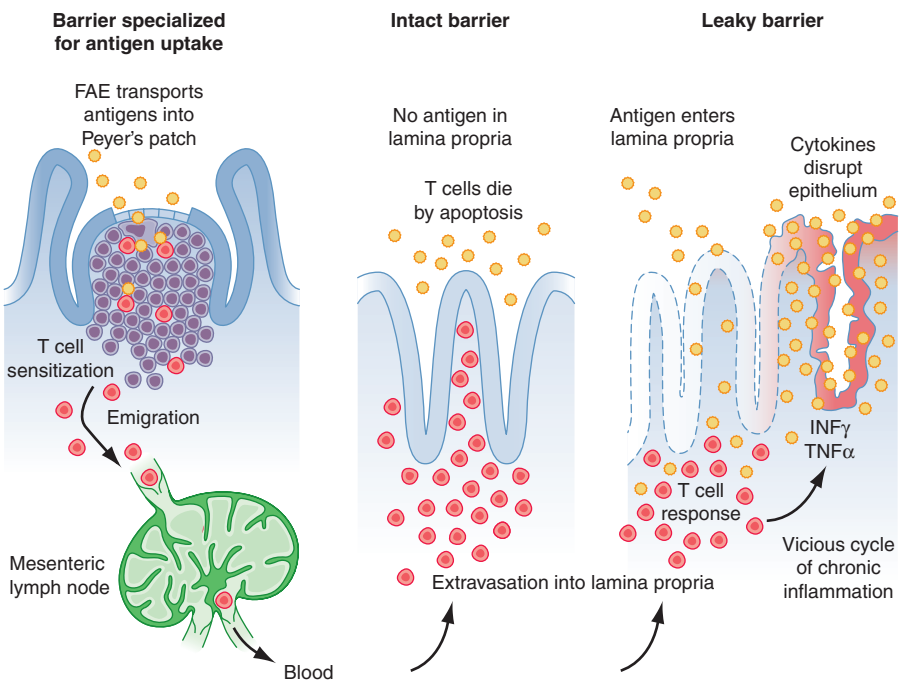


FIGURE 1-9

Increased epithelial permeability may be important in the development of chronic gut T cell–mediated inflammation. CD4 T cells activated by gut antigens in Peyer's patches migrate to the LP. In healthy individuals, these cells die by apoptosis. Increased epithelial permeability may allow sufficient antigen to enter the LP to trigger T cell activation, breaking tolerance mediated by immunosuppressive cytokines and perhaps T regulatory cells. Proinflammatory cytokines then further increase epithelial permeability, setting up a vicious cycle of chronic inflammation. (*From T MacDonald, G Monteleone: Science 307:1924, 2005; with permission.*)

THE CELLULAR AND MOLECULAR CONTROL OF PROGRAMMED CELL DEATH

The process of apoptosis (programmed cell death) plays a crucial role in regulating normal immune responses to antigen. In general, a wide variety of stimuli trigger one of several apoptotic pathways to eliminate microbe-infected cells, eliminate cells with damaged DNA, or eliminate activated immune cells that are no longer needed (Fig. 1-10). The largest known family of "death receptors" is the tumor necrosis factor receptor (TNF-R) family [TNF-R1, TNF-R2, Fas (CD95), death receptor 3 (DR3), death receptor 4 [DR4, TNF-related apoptosis-including ligand receptor 1 (TRAIL-R1)], and death receptor 5 (DR5, TRAIL-R2)]; their ligands are all in the TNF-α family. Binding of ligands to these death receptors leads to a signaling cascade that involves activation of the *caspase* family of molecules that leads

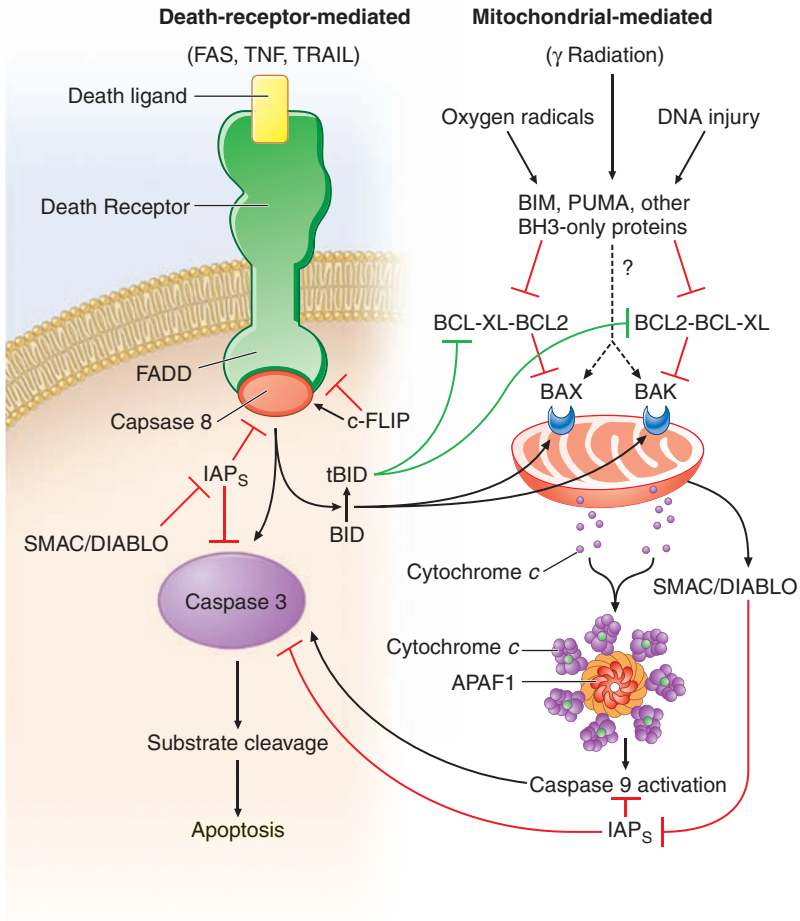


FIGURE 1-10

Pathways of Cellular Apoptosis. There are two major pathways of apoptosis: the death-receptor pathway, which is mediated by activation of death receptors, and the BCL2-regulated mitochondrial pathway, which is mediated by noxious stimuli that ultimately lead to mitochondrial injury. Ligation of death receptors recruits the adaptor protein FAS-associated death domain (FADD). FADD in turn recruits caspase 8, which ultimately activates caspase 3, the key "executioner" caspase. Cellular FLICE-inhibitory protein (c-FLIP) can either inhibit or potentiate binding of FADD and caspase 8, depending on its concentration. In the intrinsic pathway, proapoptotic BH3 proteins are activated by noxious stimuli, which interact with and inhibit antiapoptotic BCL2 or BCL-XL. Thus, BAX and BAK are free to induce mitochondrial permeabilization with release of cytochrome *c*, which ultimately results in the activation of caspase 9 through the apoptosome. Caspase 9 then activates caspase 3. SMAC/DIABLO is also released after mitochondrial permeabilization and acts to block the action of inhibitors of apoptosis protein (IAPs), which inhibit caspase activation. There is potential cross-talk between the two pathways, which is mediated by the truncated form of BID (tBID) that is produced by caspase 8–mediated BID cleavage; tBID acts to inhibit the BCL2-BCL-XL pathway and to activate BAX and BAK. There is debate (indicated by the question mark) as to whether proapoptotic BH3 molecules (e.g., BIM and PUMA) act directly on BAX and BAK to induce mitochondrial permeability or whether they act only on BCL2-BCL-XL. APAF1, apoptotic protease-activating factor 1; BH3, BCL homologue; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand. (*From RS Hotchkiss et al: N Engl J Med 361:1570, 2009; with permission.*)

to DNA cleavage and cell death. Two other pathways of programmed cell death involve nuclear *p53* in the elimination of cells with abnormal DNA and *mitochondrial cytochrome c* to induce cell death in damaged cells (Fig. 1-10). A number of human diseases have now been described that result from, or are associated with, mutated apoptosis genes **(Table 1-15)**. These include mutations in the Fas and Fas ligand genes in autoimmune and lymphoproliferation syndromes, and multiple associations of mutations in genes in the apoptotic pathway with malignant syndromes.

MECHANISMS OF IMMUNE-MEDIATED DAMAGE TO MICROBES OR HOST TISSUES

Several responses by the host innate and adaptive immune systems to foreign microbes culminate in rapid and efficient elimination of microbes. In these scenarios, the classic weapons of the adaptive immune system (T cells, B cells) interface with cells (macrophages, dendritic cells, NK cells, neutrophils, eosinophils, basophils) and soluble products (microbial peptides, pentraxins, complement and coagulation systems) of the innate immune system.

There are five general phases of host defenses: (1) migration of leukocytes to sites of antigen localization; (2) antigen-nonspecific recognition of pathogens by macrophages and other cells and systems of the innate immune system; (3) specific recognition of foreign antigens mediated by T and B lymphocytes; (4) amplification of the inflammatory response with recruitment of specific and nonspecific effector cells by complement components, cytokines, kinins, arachidonic acid metabolites, and mast cell–basophil products; and (5) macrophage, neutrophil, and lymphocyte participation in destruction of antigen with ultimate removal of antigen particles by phagocytosis (by macrophages or neutrophils) or by direct cytotoxic mechanisms (involving macrophages, neutrophils, DCs, and lymphocytes).

TABLE 1-15

IMMUNE SYSTEM MOLECULE DEFECTS IN ANIMALS OR HUMANS THAT CAUSE AUTOIMMUNE OR MALIGNANT SYNDROMES

PROTEIN	DEFECT	DISEASE OR SYNDROME	OBSERVATION IN ANIMAL MODELS OR HUMANS
Cytokines and Signaling Proteins			
Tumor necrosis factor (TNF) α	Overexpression	Inflammatory bowel disease (IBD), arthritis, vasculitis	Mice
TNF-α	Underexpression	Systemic lupus erythematosus (SLE)	Mice
Interleukin-1-receptor antagonist	Underexpression	Arthritis	Mice
IL-2	Overexpression	IBD	Mice
IL-7	Overexpression	IBD	Mice
IL-10	Overexpression	IBD	Mice
IL-2 receptor	Overexpression	IBD	Mice
IL-10 receptor	Overexpression	IBD	Mice
IL-3	Overexpression	Demyelinating syndrome	Mice
Interferon-δ	Overexpression in skin	SLE	Mice
STAT-3	Underexpression	IBD	Mice
STAT-4	Overexpression	IBD	Mice
Transforming growth factor (TGF) β	Underexpression	Systemic wasting syndrome and IBD	Mice
TGF-β receptor in T cells	Underexpression	SLE	Mice
Programmed death (PD-1)	Underexpression	SLE-like syndrome	Mice
Cytotoxic T lymphocyte, antigen-4 (CTLA-4)	Underexpression	Systemic lymphoproliferative disease	Mice
IL-10	Underexpression	IBD (mouse) Type 1 diabetes, thyroid disease, primary (human)	Mice and humans

(*continued*)

TABLE 1-15

IMMUNE SYSTEM MOLECULE DEFECTS IN ANIMALS OR HUMANS THAT CAUSE AUTOIMMUNE OR MALIGNANT SYNDROMES (*CONTINUED*)

APOPTOSIS PROTEIN	DEFECT	DISEASE OR SYNDROME	OBSERVATION IN ANIMAL MODELS OR HUMANS
Major Histocompatibility Locus Molecules*			
HLA B27	Allele expression or overexpression	Inflammatory bowel disease	Rats and humans
Complement deficiency of C1, 2, 3 or 4	Underexpression		Humans
LIGHT (TNF superfamily 14)	Overexpression	Systemic lymphoproliferative (mouse) and autoimmunity	Mice
HLA class II DQB10301, DQB10302	Allele expression	Juvenile-onset diabetes	Humans
HLA class II DQB10401, DQB10402	Allele expression	Rheumatoid arthritis	Humans
HLA class I B27	Allele expression	Ankylosing spondylitis, IBD	Rats and humans
Apoptosis Proteins			
TNF receptor 1 (TNF-R1)	Underexpression	Familial periodic fever syndrome	Humans
Fas (CD95; Apo-1)	Underexpression	Autoimmune lymphoproliferative syndrome type 1 (ALPS 1); malignant lymphoma; bladder cancer	Humans
Fas ligand	Underexpression	SLE (only one case identified)	Humans
Perforin	Underexpression	Familial hemophagocytic lymphohistiocytosis (FHL)	Humans
Caspase 10	Underexpression	Autoimmune lymphoproliferative syndrome type II (ALPS II)	Humans
bcl-10	Underexpression	Non-Hodgkin's lymphoma	Humans
P53	Underexpression	Various malignant neoplasms	Humans
Bax	Underexpression	Colon cancer; hematopoietic malignancies	Humans
bcl-2	Underexpression	Non-Hodgkin's lymphoma	Humans
c-IAP2	Underexpression	Low-grade MALT lymphoma	Humans
NAIP1	Underexpression	Spinal muscular atrophy	Humans

*Many autoimmune diseases are associated with a myriad of major compatibility complex gene allele (HLA) types. They are presented here as examples.

Abbreviation: MALT, mucosa-associated lymphoid tissue.

Source: Adapted from L Mullauer et al: Mutat Res 488:211, 2001 and A Davidson, B Diamond: N Engl J Med 345:240, 2001; with permission.

Under normal circumstances, orderly progression of host defenses through these phases results in a well-controlled immune and inflammatory response that protects the host from the offending antigen. However, dysfunction of any of the host defense systems can damage host tissue and produce clinical disease. Furthermore, for certain pathogens or antigens, the normal immune response itself might contribute substantially to the tissue damage. For example, the immune and inflammatory response in the brain to certain pathogens such as *M. tuberculosis* may be responsible for much of the morbidity rate of this disease in that organ system. In addition, the morbidity rate associated with certain pneumonias such as that caused by *Pneumocystis jiroveci* may be associated more with inflammatory infiltrates than with the tissue-destructive effects of the microorganism itself.

The molecular basis of lymphocyte–endothelial cell interactions

The control of lymphocyte circulatory patterns between the bloodstream and peripheral lymphoid organs operates at the level of lymphocyte–endothelial cell interactions to control the specificity of lymphocyte subset entry into organs. Similarly, lymphocyte–endothelial cell interactions regulate the entry of lymphocytes into inflamed tissue. Adhesion molecule expression on lymphocytes and endothelial cells regulates the retention and subsequent egress of lymphocytes within tissue sites of antigenic stimulation, delaying cell exit from tissue and preventing reentry into the circulating lymphocyte pool **(Fig. 1-11)**. All types of lymphocyte migration

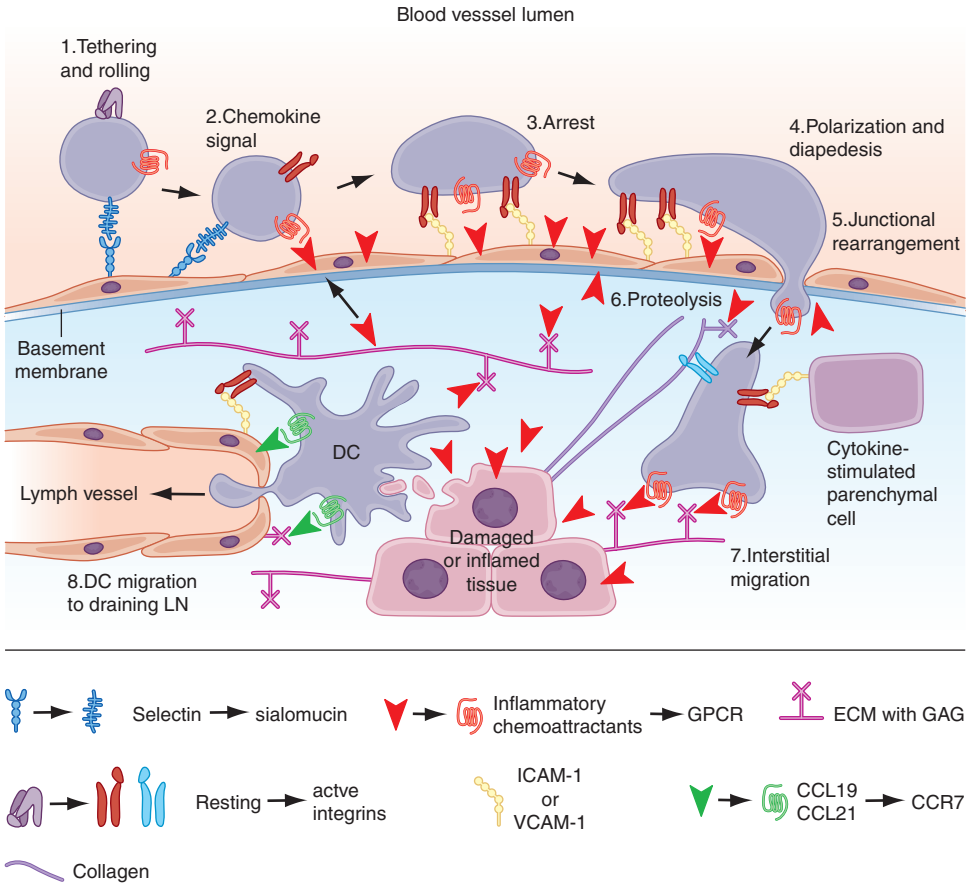


FIGURE 1-11

Key migration steps of immune cells at sites of inflammation. Inflammation due to tissue damage or infection induces the release of cytokines (not shown) and inflammatory chemoattractants (red arrowheads) from distressed stromal cells and "professional" sentinels, such as mast cells and macrophages (not shown). The inflammatory signals induce upregulation of endothelial selectins and immunoglobulin "superfamily" members, particularly ICAM-1 and/or VCAM-1. Chemoattractants, particularly chemokines, are produced by or translocated across venular endothelial cells (red arrow) and are displayed in the lumen to rolling leukocytes. Those leukocytes that express the appropriate set of trafficking molecules undergo a multistep adhesion cascade (steps 1–3) and then polarize and move by diapedesis across the venular wall (steps 4 and 5). Diapedesis involves transient disassembly of endothelial junctions and penetration through the underlying basement membrane (step 6). Once in the extravascular (interstitial) space, the migrating cell uses different integrins to gain "footholds" on collagen fibers and other ECM molecules, such as laminin and fibronectin, and on inflammation-induced ICAM-1 on the surface of parenchymal cells (step 7). The migrating cell receives guidance cues from distinct sets of chemoattractants, particularly chemokines, which may be immobilized on glycosaminoglycans (GAG) that "decorate" many ECM molecules and stromal cells. Inflammatory signals also induce tissue DCs to undergo maturation. Once DCs process material from damaged tissues and invading pathogens, they upregulate CCR7, which allows them to enter draining lymph vessels that express the CCR7 ligand CCL21 (and CCL19). In lymph nodes (LN), these antigen-loaded mature DCs activate naïve T cells and expand pools of effector lymphocytes, which enter the blood and migrate back to the site of inflammation. T cells in tissue also use this CCR7-dependent route to migrate from peripheral sites to draining lymph nodes through afferent lymphatics. (*Adapted from AD Luster et al: Nat Immunol 6:1182, 2005; with permission from Macmillan Publishers Ltd. Copyright 2005.*)

begin with lymphocyte attachment to specialized regions of vessels, termed *high endothelial venules* (HEVs). An important concept is that adhesion molecules do not generally bind their ligand until a conformational change (ligand activation) occurs in the adhesion molecule that allows ligand binding. Induction of a conformation-dependent determinant on an adhesion molecule can be accomplished by cytokines or via ligation of other adhesion molecules on the cell.

The first stage of lymphocyte–endothelial cell interactions, *attachment and rolling*, occurs when lymphocytes leave the stream of flowing blood cells in a postcapillary venule and roll along venule endothelial cells (Fig. 1-11). Lymphocyte rolling is mediated by the l-selectin molecule (LECAM-1, LAM-1, CD62L) and slows cell transit time through venules, allowing time for activation of adherent cells.

The second stage of lymphocyte–endothelial cell interactions, *firm adhesion with activation-dependent stable arrest*, requires stimulation of lymphocytes by chemoattractants or by endothelial cell–derived cytokines. Cytokines thought to participate in adherent cell activation include members of the IL-8 family, platelet-activation factor, leukotriene B_4, and C5a. In addition, HEVs express chemokines, SLC (CCL21) and ELC (CCL19), which participate in this process. Following activation by chemoattractants, lymphocytes shed l-selectin from the cell surface and upregulate cell CD11b/18 (MAC-1) or CD11a/18 (LFA-1) molecules, resulting in firm attachment of lymphocytes to HEVs.

Lymphocyte homing to peripheral lymph nodes involves adhesion of L-selectin to glycoprotein HEV ligands collectively referred to as *peripheral node addressin (PNAd)*, whereas homing of lymphocytes to intestine Peyer's patches primarily involves adhesion of the $\alpha4,\beta7$ integrin to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the Peyer's patch HEVs. However, for migration to mucosal Peyer's patch lymphoid aggregates, naïve lymphocytes primarily use L-selectin, whereas memory lymphocytes use $\alpha4,\beta7$ integrin. $\alpha4,\beta1$ Integrin (CD49d/CD29, VLA-4)–VCAM-1 interactions are important in the initial interaction of memory lymphocytes with HEVs of multiple organs in sites of inflammation **(Table 1-16)**.

The third stage of leukocyte emigration in HEVs is *sticking and arrest*. Sticking of the lymphocyte to endothelial cells and arrest at the site of sticking are mediated predominantly by ligation of $\alpha1,\beta2$ integrin LFA-1 to the integrin ligand ICAM-1 on HEVs. While the first three stages of lymphocyte attachment to HEVs take only a few seconds, the fourth stage of lymphocyte emigration, *transendothelial migration*, takes ~10 min. Although the molecular mechanisms that control lymphocyte transendothelial migration are not fully characterized, the HEV CD44 molecule and molecules of the HEV glycocalyx (extracellular matrix) are thought to play important regulatory roles in this process (Fig. 1-11). Finally, expression of matrix metalloproteases capable of digesting the subendothelial basement membrane, rich in nonfibrillar collagen, appears to be required for the penetration of lymphoid cells into the extravascular sites.

Abnormal induction of HEV formation and use of the molecules discussed earlier have been implicated in the induction and maintenance of inflammation in a number of chronic inflammatory diseases. In animal models of Type 1 diabetes mellitus, MAdCAM-1 and GlyCAM-1 have been shown to be highly expressed on HEVs in inflamed pancreatic islets, and treatment of these animals with inhibitors of L-selectin and $\alpha4$ integrin function blocked the development of Type 1 diabetes mellitus. A similar role for abnormal induction of the adhesion molecules of lymphocyte emigration has been suggested in *rheumatoid arthritis* (Chap. 6), *Hashimoto's thyroiditis*, *Graves' disease*, *multiple sclerosis*, *Crohn's disease*, and *ulcerative colitis*.

Immune-complex formation

Clearance of antigen by immune-complex formation between antigen, complement, and antibody is a highly effective mechanism of host defense. However, depending on the level of immune complexes formed and their physicochemical properties, immune complexes may or may not result in host and foreign cell damage. After antigen exposure, certain types of soluble antigen-antibody complexes freely circulate and, if not cleared by the reticuloendothelial system, can be deposited in blood vessel walls and in other tissues such as renal glomeruli and cause *vasculitis* or *glomerulonephritis* syndromes (Chap. 11). Deficiencies of early complement components are associated with inefficient clearance of immune complexes and immune complex mediated tissue damage in autoimmune syndromes, while deficiencies of the later complement components are associated with susceptibility to recurrent neisseria infections **(Table 1-17)**.

Immediate-type hypersensitivity

Helper T cells that drive antiallergen IgE responses are usually T_H2-type inducer T cells that secrete IL-4, IL-5, IL-6, and IL-10. Mast cells and basophils have high-affinity receptors for the Fc portion of IgE (FcRI), and cell-bound antiallergen IgE effectively "arms" basophils and mast cells. Mediator release is triggered by antigen (allergen) interaction with Fc receptor–bound IgE, the mediators released are responsible for the pathophysiologic changes of *allergic diseases* (Table 1-12). Mediators released from mast cells and basophils can be divided into three broad functional

TABLE 1-16

TRAFFICKING MOLECULES INVOLVED IN INFLAMMATORY DISEASE PROCESSES

		PROPOSED LEUKOCYTE RECEPTORS FOR ENDOTHELIAL TRAFFIC SIGNALS		
DISEASE	**KEY EFFECTOR CELL**	**L-SELECTIN, LIGAND**	**GPCR**	**INTEGRIN[a]**
Acute Inflammation				
Myocardial infarction	Neutrophil	PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
Stroke	Neutrophil	L-Selectin, PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
Ischemia-reperfusion	Neutrophil	PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
T_H1 Inflammation				
Atherosclerosis	Monocyte	PSGL-1	CCR1, CCR2, BLT1, CXCR2, CX3CR1	VLA-4
	T_H1	PSGL-1	CXCR3, CCR5	VLA-4
Multiple sclerosis	T_H1	PSGL-1 (?)	CXCR3, CXCR6	VLA-4, LFA-1
	Monocyte	PSGL-1 (?)	CCR2, CCR1	VLA-4, LFA-1
Rheumatoid arthritis	Monocyte	PSGL-1	CCR1, CCR2	VLA-1, VLA-2, VLA-4, LFA-1
	T_H1	PSGL-1	CXCR3, CXCR6	VLA-1, VLA-2, VLA-4, LFA-1
	Neutrophil	L-Selectin, PSGL-1	CXCR2, BLT1	LFA-1[b]
Psoriasis	Skin-homing T_H1	CLA	CCR4, CCR10, CXCR3	VLA-4[c], LFA-1
Crohn disease	Gut-homing T_H1	PSGL-1	CCR9, CXCR3	$\alpha4$, $\beta7$, LFA-1
Type I diabetes	T_H1	PSGL-1 (?)	CCR4, CCR5	VLA-4, LFA-1
	CD8	L-Selectin (?), PSGL-1 (?)	CXCR3	VLA-4, LFA-1
Allograft rejection	CD8	PSGL-1	CXCR3, CX3CR1, BLT1	VLA-4, LFA-1
	B cell	L-Selectin, PSGL-1	CXCR5, CXCR4	VLA-4, LFA-1
Hepatitis	CD8	PSGL-1	CXCR3, CCR5, CXCR6	VLA-4
Lupus	T_H1	None	CXCR6	VLA-4[d]
	Plasmacytoid DC	L-Selectin, CLA	CCR7, CXCR3, ChemR23	LFA-1, Mac-1
	B cell	CLA (?)	CXCR5, CXCR4	LFA-1
T_H2 Inflammation				
Asthma	T_H2	PSGL-1	CCR4, CCR8, BLT1	LFA-1
	Eosinophil	PSGL-1	CCR3, PAFR, BLT1	VLA-4, LFA-1
	Mast cells	PSGL-1	CCR2, CCR3, BLT1	VLA-4, LFA-1
Atopic dermatitis	Skin-homing T_H2	CLA	CCR4, CCR10	VLA-4, LFA-1

[a]Various β_1 integrins have been linked in different ways in basal lamina and interstitial migration of distinct cell types and inflammatory settings.
[b]In some settings, Mac-1 has been linked to transmigration.
[c]CD44 can act in concert with VLA-4 in particular models of leukocyte arrest.
[d]T_H2 cells require VAP-1 to traffic to inflamed liver.
Source: From AD Luster et al: Nat Immunol 6:1182, 2005; with permission from Macmillan Publishers Ltd. Copyright 2005.

types: (1) those that increase vascular permeability and contract smooth muscle (histamine, platelet-activating factor, SRS-A, BK-A), (2) those that are chemotactic for or activate other inflammatory cells (ECF-A, NCF, leukotriene B_4), and (3) those that modulate the release of other mediators (BK-A, platelet-activating factor).

Cytotoxic reactions of antibody

In this type of immunologic injury, complement-fixing (C1-binding) antibodies against normal or foreign cells or tissues (IgM, IgG1, IgG2, IgG3) bind complement via the classic pathway and initiate a sequence of events similar to that initiated by immune-complex deposition,

TABLE 1-17

COMPLEMENT DEFICIENCIES AND ASSOCIATED DISEASES

COMPONENT	ASSOCIATED DISEASES
Classic Pathway	
Clq, Clr, Cls, C4	Immune-complex syndromes,* pyogenic infections
C2	Immune-complex syndromes,* few with pyogenic infections
C1 Inhibitor	Rare immune-complex disease, few with pyogenic infections
C3 and Alternative Pathway C3	
C3	Immune-complex syndromes,* pyogenic infections
D	Pyogenic infections
Properdin	*Neisseria* infections
I	Pyogenic infections
H	Hemolytic uremic syndrome
Membrane Attack Complex	
C5, C6, C7, C8	Recurrent *Neisseria* infections, immune-complex disease
C9	Rare *Neisseria* infections

*Immune-complex syndromes include systemic lupus erythematosus (SLE) and SLE-like syndromes, glomerulonephritis, and vasculitis syndromes.

Source: After JA Schifferli, DK Peters: Lancet 88:957, 1983. Copyright 1983, with permission from Elsevier.

resulting in cell lysis or tissue injury. Examples of antibody-mediated cytotoxic reactions include red cell lysis in *transfusion reactions*, *Goodpasture's syndrome* with anti–glomerular basement membrane antibody formation, and *pemphigus vulgaris* with antiepidermal antibodies inducing blistering skin disease.

Classic delayed-type hypersensitivity reactions

Inflammatory reactions initiated by mononuclear leukocytes and not by antibody alone have been termed *delayed-type hypersensitivity reactions*. The term *delayed* has been used to contrast a secondary cellular response that appears 48–72 h after antigen exposure with an *immediate* hypersensitivity response generally seen within 12 h of antigen challenge and initiated by basophil mediator release or preformed antibody. For example, in an individual previously infected with *M. tuberculosis* organisms, intradermal placement of tuberculin purified-protein derivative as a skin test challenge results in an indurated area of skin at 48–72 h, indicating previous exposure to tuberculosis.

The cellular events that result in classic delayed-type hypersensitivity responses are centered around T cells (predominantly, though not exclusively, IFN-γ, IL-2, and TNF-α-secreting T_H1-type helper T cells) and macrophages. Recently NK cells have been suggested to play a major role in the form of delayed hypersensitivity that occurs following skin contact with immunogens. First, local immune and inflammatory responses at the site of foreign antigen upregulate endothelial cell adhesion molecule expression, promoting the accumulation of lymphocytes at the tissue site. In the general schemes outlined in Figs. 1-2 and 1-3, antigen is processed by dendritic cells and presented to small numbers of CD4+ T cells expressing a TCR specific for the antigen. IL-12 produced by APCs induces T cells to produce IFN-γ (T_H1 response). Macrophages frequently undergo epithelioid cell transformation and fuse to form multinucleated giant cells in response to IFN-γ. This type of mononuclear cell infiltrate is termed *granulomatous inflammation*. Examples of diseases in which delayed-type hypersensitivity plays a major role are fungal infections (*histoplasmosis*), mycobacterial infections (*tuberculosis*, *leprosy*), chlamydial infections (*lymphogranuloma venereum*), helminth infections (*schistosomiasis*), reactions to toxins (*berylliosis*), and hypersensitivity reactions to organic dusts (*hypersensitivity pneumonitis*). In addition, delayed-type hypersensitivity responses play important roles in tissue damage in autoimmune diseases such as *rheumatoid arthritis*, *giant cell arteritis*, and granulomatosis with polyangiitis (Wegener's) (Chaps. 6 and 11).

CLINICAL EVALUATION OF IMMUNE FUNCTION

Clinical assessment of immunity requires investigation of the four major components of the immune system that participate in host defense and in the pathogenesis of autoimmune diseases: (1) humoral immunity (B cells); (2) cell-mediated immunity (T cells, monocytes); (3) phagocytic cells of the reticuloendothelial system (macrophages), as well as polymorphonuclear leukocytes; and (4) complement. Clinical problems that require an evaluation of immunity include chronic infections, recurrent infections, unusual infecting agents, and certain autoimmune syndromes. The type of clinical syndrome under evaluation can provide information regarding possible immune defects. Defects in cellular immunity generally result in viral, mycobacterial, and fungal infections. An extreme example of deficiency in cellular immunity is AIDS. Antibody deficiencies result in recurrent bacterial infections, frequently with organisms such as *S. pneumoniae* and *Haemophilus influenzae*. Disorders of phagocyte function are frequently manifested by recurrent skin infections, often due to *Staphylococcus aureus*. Finally, deficiencies of early and late complement components are associated with autoimmune phenomena and recurrent *Neisseria* infections (Table 1-17).

IMMUNOTHERAPY

Many therapies for autoimmune and inflammatory diseases involve the use of nonspecific immune-modulating or immunosuppressive agents such as glucocorticoids or cytotoxic drugs. The goal of development of new treatments for immune-mediated diseases is to design ways to specifically interrupt pathologic immune responses, leaving nonpathologic immune responses intact. Novel ways to interrupt pathologic immune responses that are under investigation include the use of anti-inflammatory cytokines or specific cytokine inhibitors as anti-inflammatory agents, the use of monoclonal antibodies against T or B lymphocytes as therapeutic agents, the induction of anergy by administration of soluble CTLA-4 protein, the use of intravenous Ig for certain infections and immune complex–mediated diseases, the use of specific cytokines to reconstitute components of the immune system, and bone marrow transplantation to replace the pathogenic immune system with a more normal immune system. In particular, the use of a monoclonal antibody to B cells (rituximab, anti-CD20 MAb) is approved in the United States for the treatment of non-Hodgkin's lymphoma in combination with methotrexate, for treatment of adult patients with severe rheumatoid arthritis resistant to TNF-α inhibitors (Chap. 6) and in granulomatosis with polyangiitis (Wegener's) (Chap. 11).

Cytokines and cytokine inhibitors

A humanized mouse anti-TNF-α monoclonal antibody (MAb) has been shown to be effective in both rheumatoid arthritis and ulcerative colitis. Use of anti-TNF-α antibody therapy has resulted in clinical improvement in patients with these diseases and has opened the way for targeting TNF-α to treat other severe forms of autoimmune and/or inflammatory disease. Blockage of TNF has now been recognized to be effective in the treatment of a number of inflammatory diseases. For example, the anti-TNF-α MAb (infliximab) has been approved by the FDA for treatment of patients with rheumatoid arthritis. It has now also been approved for ankylosing spondylitis, psoriatic arthritis and psoriasis, ulcerative colitis, and adult and pediatric Crohn's disease.

Other cytokine inhibitors are recombinant soluble TNF-α receptor (R) fused to human Ig and Anakinra (soluble *IL-1 receptor antagonist*, or IL-1 ra). The treatment of autoinflammatory syndromes (Table 1-6) with recombinant IL-1 receptor antagonist can prevent symptoms in these syndromes, since the overproduction of IL-1β is a hallmark of these diseases. Soluble TNF-αR (etanercept) and IL-1 ra act to inhibit the activity of pathogenic cytokines in rheumatoid arthritis, i.e., TNF-α and IL-1, respectively. Similarly, anti-IL-6, IFN-β, and IL-11 act to inhibit pathogenic proinflammatory cytokines. Anti-IL-6 inhibits IL-6 activity, while IFN-β and IL-11 decrease IL-1 and TNF-α production.

Of particular note has been the successful use of IFN-γ in the treatment of the phagocytic cell defect in *chronic granulomatous disease*.

Monoclonal antibodies to T and B cells

The OKT3 MAb against human T cells has been used for several years as a T cell–specific immunosuppressive agent that can substitute for horse anti-thymocyte globulin (ATG) in the treatment of solid organ transplant rejection. OKT3 produces fewer allergic reactions than ATG but does induce human anti-mouse Ig antibody—thus limiting its use. Anti-CD4 MAb therapy has been used in trials to treat patients with rheumatoid arthritis. While inducing profound immunosuppression, anti-CD4 MAb treatment also induces susceptibility to severe infections. Treatment of patients with a MAb against the T cell molecule CD40 ligand (CD154) is under investigation to induce tolerance to organ transplants, with promising results reported in animal studies. Monoclonal antibodies to the CD25 (IL-2α) receptor (Basiliximab) are being used for treatment of graft-versus-host disease in bone marrow transplantation, and anti-CD20 MAb (rituximab) is used to treat hematologic neoplasms, autoimmune diseases, and kidney transplant rejection. The anti-IgE monoclonal antibody (omalizumab) is used for blocking antigen-specific IgE that causes *hay fever* and *allergic rhinitis*; however, side effects of anti-IgE include increased risk of anaphylaxis. Studies have shown that T_H17 cells, in addition to T_H1, are mediators of inflammation in Crohn's disease, and anti–IL-12/IL-23p40 antibody therapy has been studied as a treatment.

It is important to realize the potential risks for these immunosuppressive monoclonal antibodies. Natalizumab is a humanized IgG antibody against an α4 integrin that inhibits leukocyte migration into tissues, and has been approved for treatment of multiple sclerosis in the United States. Both it and anti-CD20 (rituximab) have been associated with the onset of progressive multifocal leukoencephalopathy (PML)—a serious and usually fatal CNS infection caused by JC polyoma virus. Efalizumab, a humanized IgG monoclonal antibody previously approved for treatment of plaque psoriasis, has now been taken off the market due to reactivation of JC virus leading to fatal PML. Thus, use of any currently approved immunosuppressant immunotherapies should be undertaken with caution and with careful monitoring of patients according to FDA guidelines.

Tolerance induction

Specific immunotherapy has moved into a new era with the introduction of soluble CTLA-4 protein into

clinical trials. Use of this molecule to block T cell activation via TCR/CD28 ligation during organ or bone marrow transplantation has showed promising results in animals and in early human clinical trials. Specifically, treatment of bone marrow with CTLA-4 protein reduces rejection of the graft in HLA-mismatched bone marrow transplantation. In addition, promising results with soluble CTLA-4 have been reported in the down-modulation of autoimmune T cell responses in the treatment of psoriasis; and it is being studied for treatment of systemic lupus erythematosus (Chap. 4).

Intravenous immunoglobulin (IVIg)

IVIg has been used successfully to block reticuloendothelial cell function and immune complex clearance in various immune cytopenias such as immune thrombocytopenia. In addition, IVIg is useful for prevention of tissue damage in certain inflammatory syndromes such as Kawasaki disease (Chap. 11) and as Ig replacement therapy for certain types of immunoglobulin deficiencies. In addition, controlled clinical trials support the use of IVIg in selected patients with graft-versus-host disease, multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome, and chronic demyelinating polyneuropathy.

Stem cell transplantation

Hematopoietic stem cell transplantation (SCT) is now being comprehensively studied to treat several autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, and scleroderma. The goal of immune reconstitution in autoimmune disease syndromes is to replace a dysfunctional immune system with a normally reactive immune cell repertoire. Preliminary results in patients with scleroderma and lupus have showed encouraging results. Controlled clinical trials in these three diseases are now being launched in the United States and Europe to compare the toxicity and efficacy of conventional immunosuppression therapy with that of myeloablative autologous SCT.

Thus, a number of recent insights into immune system function have spawned a new field of interventional immunotherapy and have enhanced the prospect for development of specific and nontoxic therapies for immune and inflammatory diseases.

CHAPTER 2

THE MAJOR HISTOCOMPATIBILITY COMPLEX

Gerald T. Nepom

THE HLA COMPLEX AND ITS PRODUCTS

The human major histocompatibility complex (MHC), commonly called the human leukocyte antigen (HLA) complex, is a 4-megabase (Mb) region on chromosome 6 (6p21.3) that is densely packed with expressed genes. The best known of these genes are the HLA class I and class II genes, whose products are critical for immunologic specificity and transplantation histocompatibility, and they play a major role in susceptibility to a number of autoimmune diseases. Many other genes in the HLA region are also essential to the innate and antigen-specific functioning of the immune system. The HLA region shows extensive conservation with the MHC of other mammals in terms of genomic organization, gene sequence, and protein structure and function.

The *HLA class I genes* are located in a 2-Mb stretch of DNA at the telomeric end of the HLA region **(Fig. 2-1)**. The classic (MHC class Ia) HLA-A, -B, and -C loci, the products of which are integral participants in the immune response to intracellular infections, tumors, and allografts, are expressed in all nucleated cells and are highly polymorphic in the population. *Polymorphism* refers to a high degree of allelic variation within a genetic locus that leads to extensive variation between different individuals expressing different alleles. More than 650 alleles at HLA-A, 1000 at HLA-B, and 360 at HLA-C have been identified in different human populations, making this the most highly polymorphic segment known within the human genome. Each of the alleles at these loci encodes a *heavy chain* (also called an α *chain*) that associates noncovalently with the nonpolymorphic light chain β_2-*microglobulin*, encoded on chromosome 15.

The nomenclature of HLA genes and their products reflects the grafting of newer DNA sequence information on an older system based on serology. Among class I genes, alleles of the HLA-A, -B, and -C loci were originally identified in the 1950s, 1960s, and 1970s by alloantisera, derived primarily from multiparous women, who in the course of normal pregnancy produce antibodies against paternal antigens expressed on fetal cells. The serologic allotypes were designated by consecutive numbers (e.g., HLA-A1, HLA-B8). Currently, under World Health Organization (WHO) nomenclature, class I alleles are given a single designation that indicates locus, serologic specificity, and sequence-based subtype. For example, HLA-A*0201 indicates subtype 1 of the serologically defined allele HLA-A2. Subtypes that differ from each other at the nucleotide but not the amino acid sequence level are designated by an extra numeral (e.g., HLA-B*07021 and HLA-B*07022 are two variants of the HLA-B702 subtype of HLA-B*07). The nomenclature of class II genes, discussed later, is made more complicated by the fact that both chains of a class II molecule are encoded by closely linked HLA-encoded loci, both of which may be polymorphic, and by the presence of differing numbers of isotypic DRB loci in different individuals. It has become clear that accurate HLA genotyping requires DNA sequence analysis, and the identification of alleles at the DNA sequence level has contributed greatly to the understanding of the role of HLA molecules as peptide-binding ligands, to the analysis of associations of HLA alleles with certain diseases, to the study of the population genetics of HLA, and to a clearer understanding of the contribution of HLA differences to allograft rejection and graft-versus-host disease. Current databases of HLA class I and class II sequences can be accessed by the Internet (e.g., from the IMGT/HLA Database, *http://www.ebi.ac.uk/imgt/hla*), and frequent updates of HLA gene lists are published in several journals.

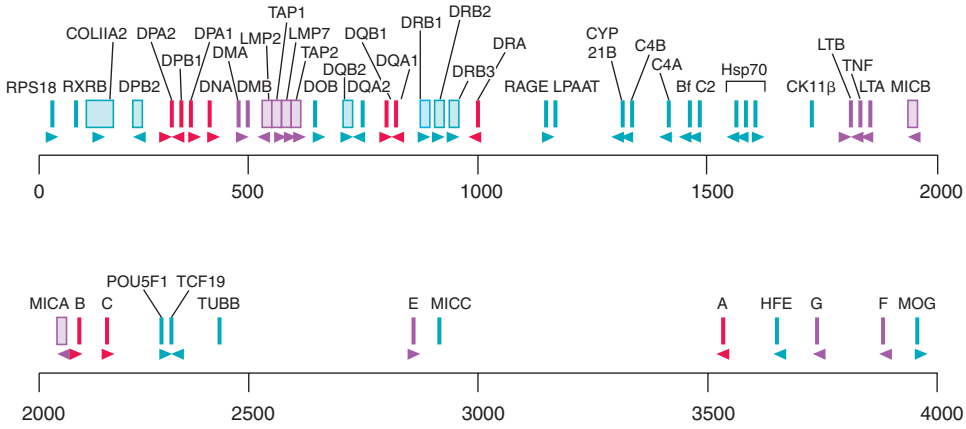


FIGURE 2-1

Physical map of the HLA region, showing the class I and class II loci, other immunologically important loci, and a sampling of other genes mapped to this region. Gene orientation is indicated by arrowheads. Scale is in kilobase (kb). The approximate genetic distance from DP to A is 3.2 cM. This includes 0.8 cM between A and B (including 0.2 cM between C and B), 0.4–0.8 cM between B and DR-DQ, and 1.6–2.0 cM between DR-DQ and DP.

The biologic significance of this MHC genetic diversity, resulting in extreme variation in the human population, is evident from the perspective of the structure of MHC molecules. As shown in **Fig. 2-2**, the MHC class I and class II genes encode MHC molecules that bind small peptides, and together this complex (pMHC; peptide-MHC) forms the ligand for recognition by T lymphocytes, through the antigen-specific T cell receptor (TCR). There is a direct link between the genetic variation and this structural interaction: The allelic changes in genetic sequence result in diversification of the peptide-binding capabilities of each MHC molecule and in differences for specific TCR binding. Thus, different pMHC complexes bind different antigens and are targets for recognition by different T cells.

The class I MHC and class II MHC structures, shown in Fig. 2-2*B*, *C*, are structurally closely related; however, there are a few key differences. While both bind peptides and present them to T cells, the binding pockets have different shapes, which influence the

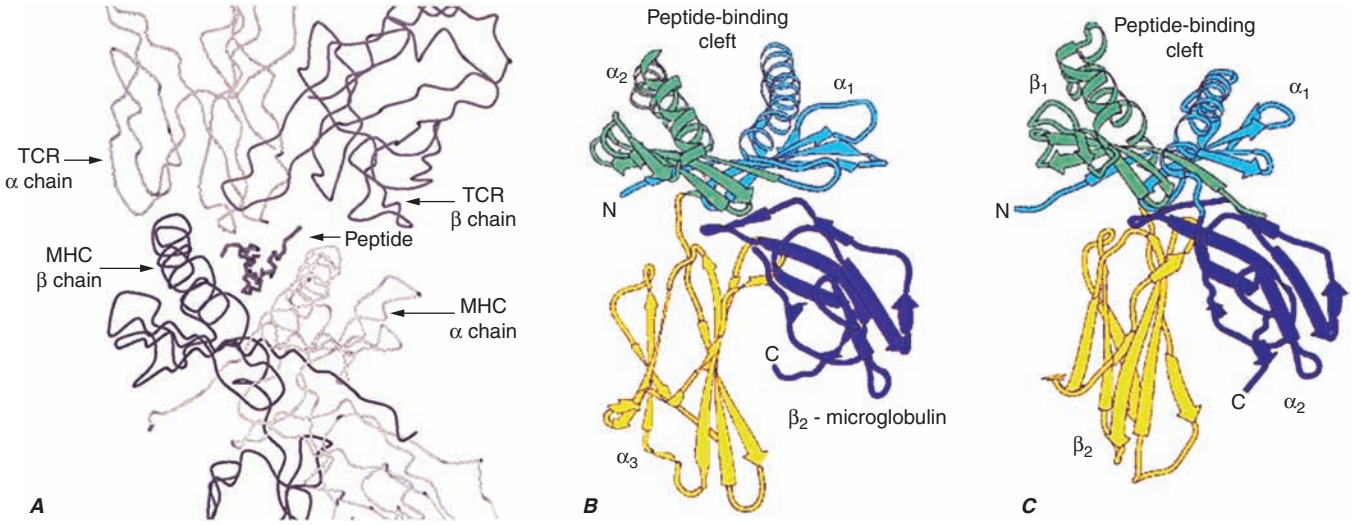


FIGURE 2-2

A. The trimolecular complex of TCR (top), MHC molecule (bottom) and a bound peptide form the structural determinants of specific antigen recognition. Other panels (***B*** and ***C***) show the domain structure of MHC class I (***B***) and class II (***C***) molecules. The α_1 and α_2 domains of class I and the α_1 and β_1 domains of class II form a β-sheet platform that forms the floor of the peptide-binding groove, and α helices that form the sides of the groove. The α_3 (***B***) and β_2 domains (***C***) project from the cell surface and form the contact sites for CD8 and CD4, respectively. (*Adapted from EL Reinhertz et al: Science 286:1913, 1999; and C Janeway et al: Immunobiology Bookshelf, 2nd ed, Garland Publishing, New York, 1997; with permission.*)

types of immune responses that result (discussed later). In addition, there are structural contact sites for T cell molecules known as CD8 and CD4, expressed on the class I or class II membrane-proximal domains, respectively. This ensures that when peptide antigens are presented by class I molecules, the responding T cells are predominantly of the CD8 class, and similarly, that T cells responding to class II pMHC complexes are predominantly CD4.

The nonclassic, or class Ib, MHC molecules, HLA-E, -F, and -G, are much less polymorphic than MHC Ia and appear to have distinct functions. The HLA-E molecule has a peptide repertoire displaying signal peptides cleaved from classic MHC class I molecules and is the major self-recognition target for the natural killer (NK) cell–inhibitory receptors NKG2A or NKG2C paired with CD94 (discussed later in this chapter and in Chap. 1). This appears to be a function of immune surveillance, as loss of MHC class I signal peptides serves as a surrogate marker for injured or infected cells, leading to release of the inhibitory signal and subsequent activation of NK cells. HLA-E can also bind and present peptides to CD8 T cells, albeit with a limited scope, as only three HLA-E alleles are known. HLA-G is expressed selectively in extravillous trophoblasts, the fetal cell population directly in contact with maternal tissues. It binds a wide array of peptides, is expressed in six different alternatively spliced forms, and provides inhibitory signals to both NK cells and T cells, presumably in the service of maintaining maternofetal tolerance; 14 HLA-G alleles have been identified. The protein product of HLA-F is found mainly intracellularly, and the function of this locus, which encodes four alleles, remains largely unknown.

Additional class I–like genes have been identified, some HLA-linked and some encoded on other chromosomes, that show only distant homology to the class Ia and Ib molecules, but share the three-dimensional class I structure. Those on chromosome 6p21 include MIC-A and MIC-B, which are encoded centromeric to HLA-B, and HLA-HFE, located 3 to 4 cM (centiMorgan) telomeric of HLA-F. MIC-A and MIC-B do not bind peptide but are expressed on gut and other epithelium in a stress-inducible manner and serve as activation signals for certain $\gamma\delta$ T cells, NK cells, CD8 T cells, and activated macrophages, acting through the activating NKG2D receptors. Sixty-seven MIC-A and 30 MIC-B alleles are known, and additional diversification comes from variable alanine repeat sequences in the transmembrane domain. Due to this structural diversity, MIC-A can be recognized as a foreign tissue target during organ transplantation, contributing to graft failure. HLA-HFE encodes the gene defective in hereditary hemochromatosis. Among the non-HLA, class I–like genes, CD1 refers to a family of molecules that present glycolipids or other nonpeptide ligands to certain T cells, including T cells with NK activity; FcRn binds IgG within lysosomes and protects it from catabolism (Chap. 1); and Zn-α_2-glycoprotein 1 binds a nonpeptide ligand and promotes catabolism of triglycerides in adipose tissue. Like the HLA-A, -B, -C, -E, -F, and -G heavy chains, each of which forms a heterodimer with β_2-microglobulin (Fig. 2-2), the class I–like molecules, HLA-HFE, FcRn, and CD1 also bind to β_2-microglobulin, but MIC-A, MIC-B, and Zn-α_2-glycoprotein 1 do not.

The *HLA class II region* is also illustrated in Fig. 2-1. Multiple class II genes are arrayed within the centromeric 1 Mb of the HLA region, forming distinct haplotypes. A *haplotype* refers to an array of alleles at polymorphic loci along a chromosomal segment. Multiple class II genes are present on a single haplotype, clustered into three major subregions: HLA-DR, -DQ, and -DP. Each of these subregions contains at least one functional alpha (A) locus and one functional beta (B) locus. Together these encode proteins that form the α and β polypeptide chains of a mature class II HLA molecule. Thus, the DRA and DRB genes encode an HLA-DR molecule; products of the *DQA1* and *DQB1* genes form an HLA-DQ molecule; and the *DPA1* and *DPB1* genes encode an HLA-DP molecule. There are several DRB genes (*DRB1*, *DRB2*, *DRB3*, etc.), so that two expressed DR molecules are encoded on most haplotypes by combining the α-chain product of the DRA gene with separate β chains. More than 530 alleles have been identified at the HLA-DRB1 locus, with most of the variation occurring within limited segments encoding residues that interact with antigens. Detailed analysis of sequences and population distribution of these alleles strongly suggest that this diversity is actively selected by environmental pressures associated with pathogen diversity.

In the DQ region, both DQA1 and DQB1 are polymorphic, with 34 DQA1 alleles and 72 DQB1 alleles. The current nomenclature is largely analogous to that discussed earlier for class I, using the convention "locus *allele." Thus, for example, subtypes of the serologically defined specificity DR4, encoded by the DRB1 locus, are termed DRB1*0401, *0402, etc. In addition to allelic polymorphism, products of different DQA1 alleles can, with some limitations, pair with products of different DQB1 alleles through both *cis* and *trans* pairing to create combinatorial complexity and expand the number of expressed class II molecules. Because of the enormous allelic diversity in the general population, most individuals are heterozygous at all of the class I and class II loci. Thus, most individuals express six classic class I molecules (two each of HLA-A, -B, and -C) and around eight class II molecules—two DP, two DR (more in the case of haplotypes with additional functional DRB genes), and up to four DQ (two *cis* and two *trans*).

OTHER GENES IN THE MHC

In addition to the class I and class II genes themselves, there are numerous genes interspersed among the HLA loci that have interesting and important immunologic functions. Our current concept of the function of MHC genes now encompasses many of these additional genes, some of which are also highly polymorphic. Indeed, direct comparison of the complete DNA sequences for eight of the entire 4-Mb MHC regions from different haplotypes show >44,000 nucleotide variations, encoding an extremely high potential for biologic diversity, and at least 97 genes located in this region are known to have coding region sequence variation. Specific examples include the TAP and LMP genes, as discussed in more detail later in this chapter, which encode molecules that participate in intermediate steps in the HLA class I biosynthetic pathway. Another set of HLA genes, DMA and DMB, perform an analogous function for the class II pathway. These genes encode an intracellular molecule that facilitates the proper complexing of HLA class II molecules with antigen (discussed later). The *HLA class III region* is a name given to a cluster of genes between the class I and class II complexes, which includes genes for the two closely related cytokines tumor necrosis factor (TNF)-α and lymphotoxin (TNF-β); the complement components C2, C4, and Bf; heat shock protein (HSP)70; and the enzyme 21-hydroxylase.

The class I genes HLA-A, -B, and -C are expressed in all nucleated cells, although generally to a higher degree on leukocytes than on nonleukocytes. In contrast, the class II genes show a more restricted distribution: HLA-DR and HLA-DP genes are constitutively expressed on most cells of the myeloid cell lineage, whereas all three class II gene families (HLA-DR, -DQ, and -DP) are inducible by certain stimuli provided by inflammatory cytokines such as interferon γ. Within the lymphoid lineage, expression of these class II genes is constitutive on B cells and inducible on human T cells. Most endothelial and epithelial cells in the body, including the vascular endothelium and the intestinal epithelium, are also inducible for class II gene expression. Thus, while these somatic tissues normally express only class I and not class II genes, during times of local inflammation they are recruited by cytokine stimuli to express class II genes as well, thereby becoming active participants in ongoing immune responses. Class II expression is controlled largely at the transcriptional level through a conserved set of promoter elements that interact with a protein known as *CIITA*. Cytokine-mediated induction of CIITA is a principal method by which tissue-specific expression of HLA gene expression is controlled. Other HLA genes involved in the immune response such as TAP and LMP, are also susceptible to upregulation by signals such as interferon γ. Sequence data for the entire HLA region can be accessed on the Internet (e.g., *http://www.sanger.ac.uk/HGP/Chr6/MHC*).

LINKAGE DISEQUILIBRIUM

In addition to extensive polymorphism at the class I and class II loci, another characteristic feature of the HLA complex is *linkage disequilibrium*. This is formally defined as a deviation from Hardy-Weinberg equilibrium for alleles at linked loci. This is reflected in the very low recombination rates between certain loci within the HLA complex. For example, recombination between DR and DQ loci is almost never observed in family studies, and characteristic haplotypes with particular arrays of DR and DQ alleles are found in every population. Similarly, the complement components C2, C4, and Bf are almost invariably inherited together, and the alleles at these loci are found in characteristic haplotypes. In contrast, there is a recombinational hotspot between DQ and DP, which are separated by 1–2 cM of genetic distance, despite their close physical proximity. Certain extended haplotypes encompassing the interval from DQ into the class I region are commonly found, the most notable being the haplotype DR3-B8-A1, which is found, in whole or in part, in 10–30% of northern European whites. It has been hypothesized that selective pressures may maintain linkage disequilibrium in HLA, but this remains to be determined. As discussed later under HLA and immunologic disease, one consequence of the phenomenon of linkage disequilibrium has been the resulting difficulty in assigning HLA-disease associations to a single allele at a single locus.

MHC STRUCTURE AND FUNCTION

Class I and class II molecules display a distinctive structural architecture, which contains specialized functional domains responsible for the unique genetic and immunologic properties of the HLA complex. The principal known function of both class I and class II HLA molecules is to bind antigenic peptides in order to present antigen to an appropriate T cell. The ability of a particular peptide to satisfactorily bind to an individual HLA molecule is a direct function of the molecular fit between the amino acid residues on the peptide with respect to the amino acid residues of the HLA molecule. The bound peptide forms a tertiary structure called the *MHC-peptide complex*, which communicates with T lymphocytes through binding to the TCR molecule. The first site of TCR-MHC-peptide interaction in the life of a T cell occurs in the thymus, where self-peptides are presented to developing thymocytes

by MHC molecules expressed on thymic epithelium and hematopoietically derived antigen-presenting cells, which are primarily responsible for positive and negative selection, respectively (Chap. 1). Thus, the population of MHC–T cell complexes expressed in the thymus shapes the TCR repertoire. Mature T cells encounter MHC molecules in the periphery both in the maintenance of tolerance (Chap. 3) and in the initiation of immune responses. The MHC-peptide-TCR interaction is the central event in the initiation of most antigen-specific immune responses, since it is the structural determinant of the specificity. For potentially immunogenetic peptides, the ability of a given peptide to be generated and bound by an HLA molecule is a primary feature of whether or not an immune response to that peptide can be generated, and the repertoire of peptides that a particular individual's HLA molecules can bind exerts a major influence over the specificity of that individual's immune response.

When a TCR molecule binds to an HLA-peptide complex, it forms intermolecular contacts with both the antigenic peptide and with the HLA molecule itself. The outcome of this recognition event depends on the density and duration of the binding interaction, accounting for a dual specificity requirement for activation of the T cell. That is, the TCR must be specific both for the antigenic peptide and for the HLA molecule. The polymorphic nature of the presenting molecules, and the influence that this exerts on the peptide repertoire of each molecule, results in the phenomenon of *MHC restriction* of the T cell specificity for a given peptide. The binding of CD8 or CD4 molecules to the class I or class II molecule, respectively, also contributes to the interaction between T cell and the HLA-peptide complex, by providing for the selective activation of the appropriate T cell.

CLASS I STRUCTURE

(Fig. 2-2*B*) As noted earlier, MHC class I molecules provide a cell-surface display of peptides derived from intracellular proteins, and they also provide the signal for self-recognition by NK cells. Surface-expressed class I molecules consist of an MHC-encoded 44-kD glycoprotein heavy chain, a non-MHC-encoded 12-kD light chain β_2-microglobulin, and an antigenic peptide, typically 8–11 amino acids in length and derived from intracellularly produced protein. The heavy chain displays a prominent peptide-binding groove. In HLA-A and -B molecules, the groove is ~3 nm in length by 1.2 nm in maximum width (30 Å × 12 Å), whereas it is apparently somewhat wider in HLA-C. Antigenic peptides are noncovalently bound in an extended conformation within the peptide-binding groove, with both N- and C-terminal ends anchored in pockets within the groove (A and F pockets, respectively) and, in many cases, with a prominent kink, or arch, approximately one-third of the way from the N-terminus that elevates the peptide main chain off the floor of the groove.

A remarkable property of peptide binding by MHC molecules is the ability to form highly stable complexes with a wide array of peptide sequences. This is accomplished by a combination of peptide sequence–independent and peptide sequence–dependent bonding. The former consists of hydrogen bond and van der Waals interactions between conserved residues in the peptide-binding groove and charged or polar atoms along the peptide backbone. The latter is dependent upon the six side pockets that are formed by the irregular surface produced by protrusion of amino acid side chains from within the binding groove. The side chains lining the pockets interact with some of the peptide side chains. The sequence polymorphism among different class I alleles and isotypes predominantly affects the residues that line these pockets, and the interactions of these residues with peptide residues constitute the sequence-dependent bonding that confers a particular sequence "motif" on the range of peptides that can bind any given MHC molecule.

CLASS I BIOSYNTHESIS

(Fig. 2-3*A*) The biosynthesis of the classic MHC class I molecules reflects their role in presenting endogenous peptides. The heavy chain is cotranslationally inserted into the membrane of the endoplasmic reticulum (ER), where it becomes glycosylated and associates sequentially with the chaperone proteins calnexin and ERp57. It then forms a complex with β_2-microglobulin, and this complex associates with the chaperone calreticulin and the MHC-encoded molecule tapasin, which physically links the class I complex to TAP, the MHC-encoded transporter associated with antigen processing. Meanwhile, peptides generated within the cytosol from intracellular proteins by the multisubunit, multicatalytic proteasome complex are actively transported into the ER by TAP, where they are trimmed by a peptidase known as *ERAAP* (ER aminopeptidase associated with antigen processing). At this point, peptides with appropriate sequence complementarity bind specific class I molecules to form complete, folded heavy chain–β_2-microglobulin–peptide trimer complexes. These are transported rapidly from the ER, through the *cis*- and *trans*-Golgi where the N-linked oligosaccharide is further processed, and thence to the cell surface.

Most of the peptides transported by TAP are produced in the cytosol by proteolytic cleavage of intracellular proteins by the multisubunit, multicatalytic proteasome, and inhibitors of the proteasome dramatically reduce expression of class I–presented antigenic peptides. A thiol-dependent oxidoreductase Erp57, which mediates disulfide bond rearrangements, also appears to play an

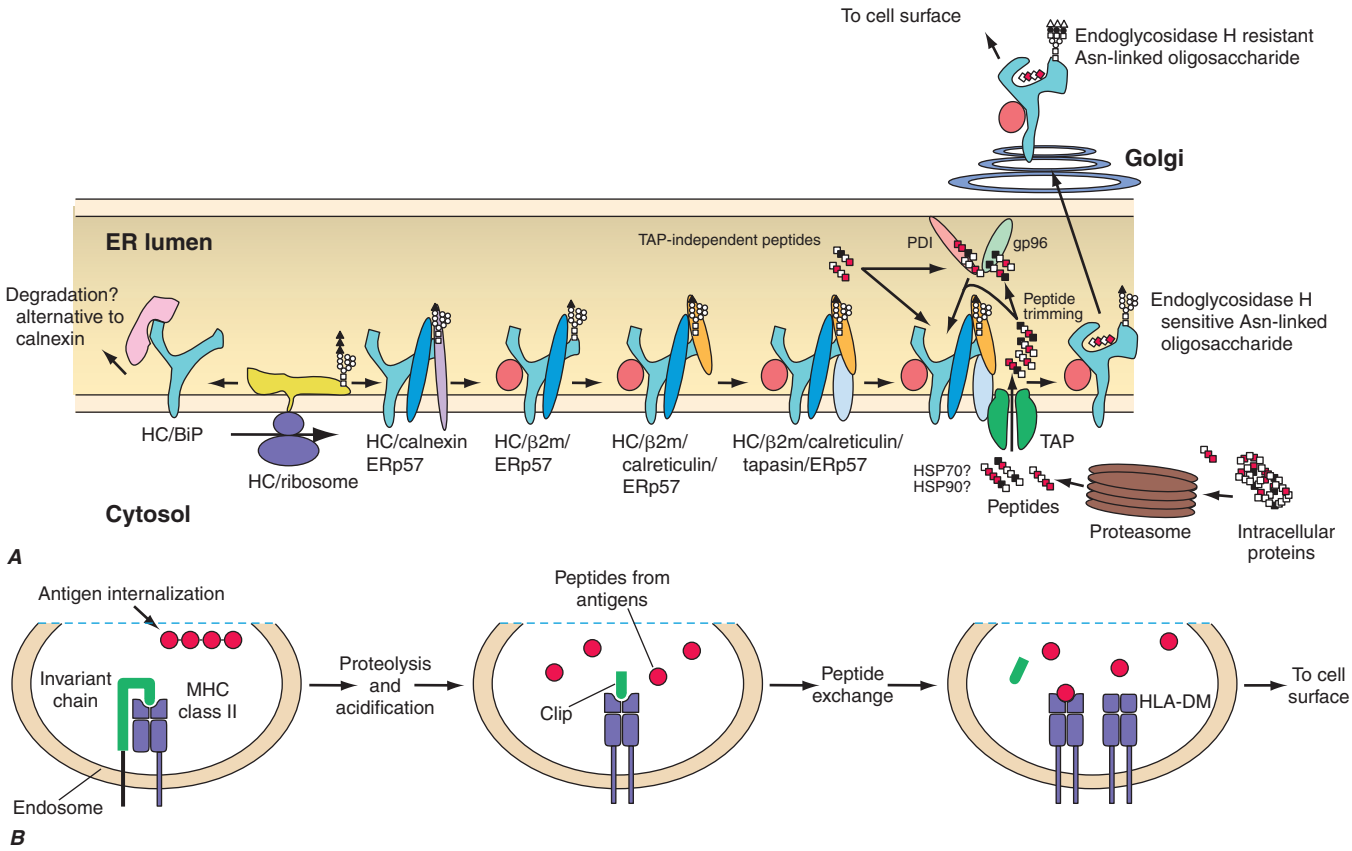


FIGURE 2-3

Biosynthesis of class I *(A)* and class II *(B)* molecules. *A.* Nascent heavy chain (HC) becomes associated with β_2-microglobulin (β2m) and peptide through interactions with a series of chaperones. Peptides generated by the proteasome are transported into the endoplasmic reticulum (ER) by TAP. Peptides undergo N-terminal trimming in the ER and become associated with chaperones, including gp96 and PDI. Once peptide binds to HC-β2m, the HC-β2m-peptide trimeric complex exits the ER and is transported by the secretory pathway to the cell surface. In the Golgi, the N-linked oligosaccharide undergoes maturation, with addition of sialic acid residues. Molecules are not necessarily drawn to scale. ***B.*** Pathway of HLA class II molecule assembly and antigen processing. After transport through the Golgi and post-Golgi compartment, the class II–invariant chain complex moves to an acidic endosome, where the invariant chain is proteolytically cleaved into fragments and displaced by antigenic peptides, facilitated by interactions with the DMA-DMB chaperone protein. This class II molecule–peptide complex is then transported to the cell surface.

important role in folding the class I–peptide complex into a stable multicomponent molecule. The MHC-encoded proteasome subunits LMP2 and LMP7 may influence the spectrum of peptides produced but are not essential for proteasome function.

CLASS I FUNCTION

Peptide antigen presentation

On any given cell, a class I molecule occurs in 100,000–200,000 copies and binds several hundred to several thousand distinct peptide species. The vast majority of these peptides are self-peptides to which the host immune system is tolerant by one or more of the mechanisms that maintain tolerance [e.g., clonal deletion in the thymus or clonal anergy or clonal ignorance in the periphery (Chaps. 1 and 3)]. However, class I molecules bearing foreign peptides expressed in a permissive immunologic context activate CD8 T cells, which, if naïve, will then differentiate into cytolytic T lymphocytes (CTLs). These T cells and their progeny, through their αβ TCRs, are then capable of Fas/CD95- and/or perforin-mediated cytotoxicity and/or cytokine secretion (Chap. 1) upon further encounter with the class I–peptide combination that originally activated it, and also with other combinations of class I molecule plus peptide that present a similar immunochemical stimulus to the TCR. As alluded to above, this phenomenon by which T cells recognize foreign antigens in the context of specific MHC alleles is termed *MHC restriction*, and the specific MHC molecule is termed the *restriction*

element. The most common source of foreign peptides presented by class I molecules is viral infection, in the course of which peptides from viral proteins enter the class I pathway. The generation of a strong CTL response that destroys virally infected cells represents an important antigen-specific defense against many viral infections (Chap. 1). In the case of some viral infections—hepatitis B, for example—CTL-induced target cell apoptosis is thought to be a more important mechanism of tissue damage than any direct cytopathic effect of the virus itself. The importance of the class I pathway in the defense against viral infection is underscored by the identification of a number of viral products that interfere with the normal class I biosynthetic pathway and thus block the immunogenetic expression of viral antigens.

Other examples of intracellularly generated peptides that can be presented by class I molecules in an immunogenic manner include peptides derived from nonviral intracellular infectious agents (e.g., *Listeria*, *Plasmodium*), tumor antigens, minor histocompatibility antigens, and certain autoantigens. There are also situations in which cell surface–expressed class I molecules are thought to acquire and present exogenously derived peptides.

HLA class I receptors and NK cell recognition

(Chap. 1) NK cells, which play an important role in innate immune responses, are activated to cytotoxicity and cytokine secretion by contact with cells that lack MHC class I expression, and NK cell activation is inhibited by cells that express MHC class I. In humans, the recognition of class I molecules by NK cells is carried out by three classes of receptor families, the killer cell–inhibitory cell receptor (KIR) family, the leukocyte Ig-like receptor (LIR) family, and the CD94/NKG2 family. The KIR family, also called CD158, is encoded on chromosome 19q13.4. KIR gene nomenclature is based on the number of domains (2D or 3D) and the presence of long (L) or short (S) cytoplasmic domains. The KIR2DL1 and S1 molecules primarily recognize alleles of HLA-C, which possess a lysine at position 80 (HLA-Cw2, -4, -5 and -6), while the KIR2DL2/S2 and KIR2DL3/S3 families primarily recognize alleles of HLA-C with asparagine at this position (HLA-Cw1,-3, -7 and -8). The KIR3D L1 and S1 molecules predominantly recognize HLA-B alleles that fall into the HLA-Bw4 class determined by residues 77–83 in the α_1 domain of the heavy chain, while the KIR3DL2 molecule is an inhibitory receptor for HLA-A*03. One of the KIR products, KIR2DL4, is known to be an activating receptor for HLA-G. The most common KIR haplotype in whites contains one activating KIR and six inhibitory KIR genes, although there is a great deal of diversity in the population, with >100 different combinations. It appears that most individuals have at least one inhibitory KIR for a self-HLA class I molecule, providing a structural basis for NK cell target specificity, which helps prevent NK cells from attacking normal cells. The importance of KIR-HLA interactions to many immune responses is illustrated by studies associating KIR3DL1 or S1 with multiple sclerosis, an autoimmune disease, but also with partial protection against HIV; in both cases consistent with a role for HLA-KIR mediated NK activation.

The LIR gene family (CD85, also called ILT) is encoded centromeric of the KIR locus on 19q13.4, and it encodes a variety of inhibitory immunoglobulin-like receptors expressed on many lymphocyte and other hematopoietic lineages. Interaction of LIR-1 (ILT2) with NK or T cells inhibits activation and cytotoxicity, mediated by many different HLA class I molecules, including HLA-G. HLA-F also appears to interact with LIR molecules, although the functional context for this is not understood.

The third family of NK receptors for HLA is encoded in the NK complex on chromosome 12p12.3-13.1 and consists of CD94 and five NKG2 genes, A/B, C, E/H, D, and F. These molecules are C-type (calcium-binding) lectins, and most function as disulfide-bonded heterodimers between CD94 and one of the NKG2 glycoproteins. The principal ligand of CD94/NKG2A receptors is the HLA-E molecule, complexed to a peptide derived from the signal sequence of classic HLA class I molecules and HLA-G. Thus, analogous to the way in which KIR receptors recognize HLA-C, the NKG2 receptor monitors self–class I expression, albeit indirectly through peptide recognition in the context of HLA-E. NKG2C, -E, and -H appear to have similar specificities but act as activating receptors. NKG2D is expressed as a homodimer and functions as an activating receptor expressed on NK cells, $\gamma\delta$ TCR T cells, and activated CD8 T cells. When complexed with an adaptor called DAP10, NKG2D recognizes MIC-A and MIC-B molecules and activates the cytolytic response. NKG2D also binds a class of molecules known as *ULBP*, structurally related to class I molecules but not encoded in the MHC. The function of NK cells in immune responses is discussed in Chap. 1.

CLASS II STRUCTURE

(Fig. 2-2*C*) A specialized functional architecture similar to that of the class I molecules can be seen in the example of a class II molecule depicted in Fig. 2-2*C*, with an antigen-binding cleft arrayed above a supporting scaffold that extends the cleft toward the external cellular environment. However, in contrast to the HLA class I molecular structure, β_2-microglobulin is not associated with class II molecules. Rather, the class II molecule is a heterodimer, composed of a 29-kD α chain and a 34-kD β chain. The amino-terminal domains of each chain

form the antigen-binding elements that, like the class I molecule, cradle a bound peptide in a groove bounded by extended α-helical loops, one encoded by the A (α chain) gene and one by the B (β chain) gene. Like the class I groove, the class II antigen-binding groove is punctuated by pockets that contact the side chains of amino acid residues of the bound peptide, but unlike the class I groove, it is open at both ends. Therefore, peptides bound by class II molecules vary greatly in length, since both the N- and C-terminal ends of the peptides can extend through the open ends of this groove. Approximately 11 amino acids within the bound peptide form intimate contacts with the class II molecule itself, with backbone hydrogen bonds and specific side chain interactions combining to provide, respectively, stability and specificity to the binding **(Fig. 2-4)**.

The genetic polymorphisms that distinguish different class II genes correspond to changes in the amino acid

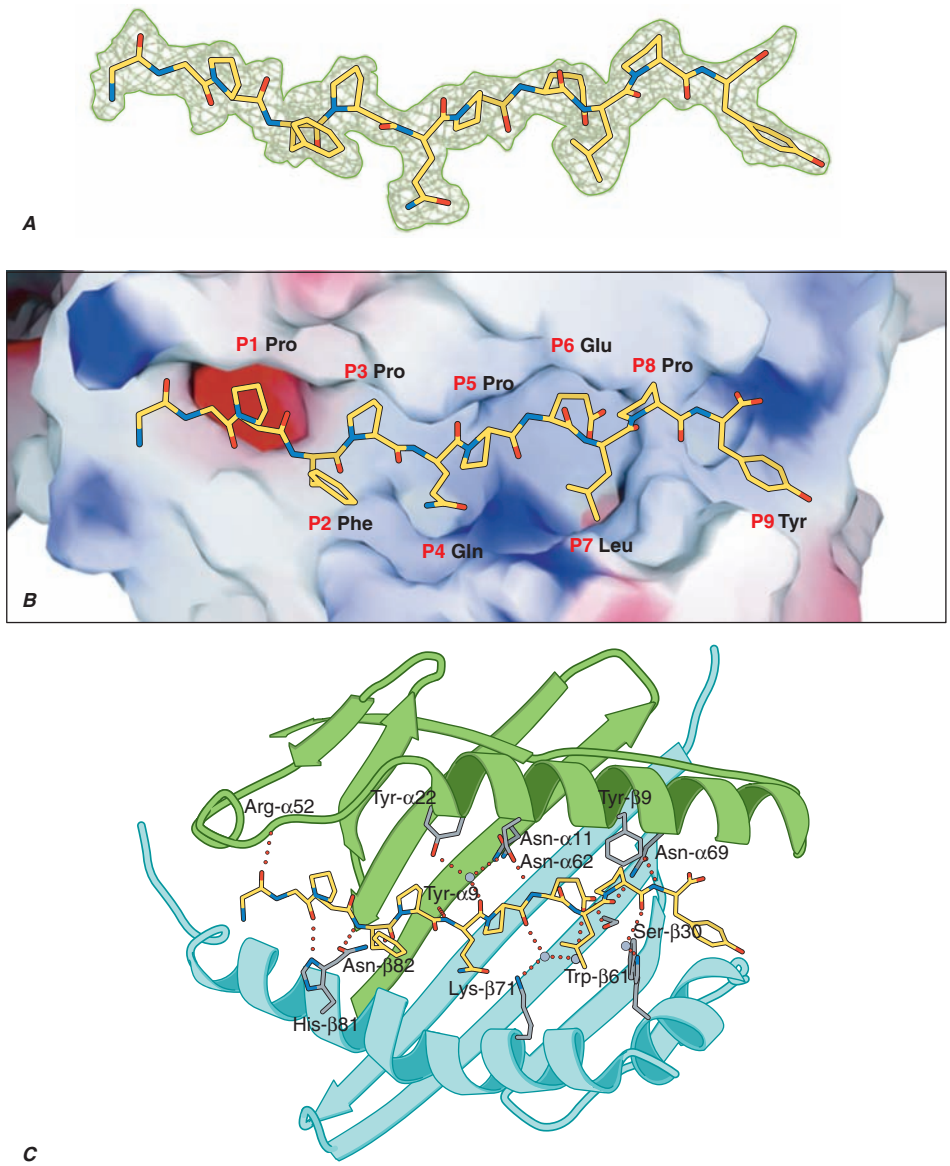


FIGURE 2-4

Specific intermolecular interactions determine peptide binding to MHC class II molecules. A short peptide sequence derived from alpha-gliadin ***(A)*** is accommodated within the MHC class II binding groove by specific interactions between peptide side chains (the P1–P9 residues illustrated in ***(B)*** and corresponding pockets in the MHC class II structure. The latter are determined by the genetic polymorphisms of the MHC gene, in this case encoding an HLA-DQ2 molecule ***(C)***. This shows the extensive hydrogen bond and salt bridge network, which tightly constrains the pMHC complex and presents the complex of antigen and restriction element for CD4 T cell recognition. (*From C Kim et al: Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease. Proc Natl Acad Sci USA 101:4175, 2004.*)

composition of the class II molecule, and these variable sites are clustered predominantly around the pocket structures within the antigen-binding groove. As with class I, this is a critically important feature of the class II molecule, which explains how genetically different individuals have functionally different HLA molecules.

BIOSYNTHESIS AND FUNCTION OF CLASS II MOLECULES

(Fig. 2-3*B*) The intracellular assembly of class II molecules occurs within a specialized compartmentalized pathway that differs dramatically from the class I pathway described earlier. As illustrated in Fig. 2-3*B*, the class II molecule assembles in the ER in association with a chaperone molecule, known as the *invariant chain*. The invariant chain performs at least two roles. First, it binds to the class II molecule and blocks the peptide-binding groove, thus preventing antigenic peptides from binding. This role of the invariant chain appears to account for one of the important differences between class I and class II MHC pathways, since it can explain why class I molecules present endogenous peptides from proteins newly synthesized in the ER but class II molecules generally do not. Second, the invariant chain contains molecular localization signals that direct the class II molecule to traffic into post-Golgi compartments known as *endosomes*, which develop into specialized acidic compartments where proteases cleave the invariant chain, and antigenic peptides can now occupy the class II groove. The specificity and tissue distribution of these proteases appear to be an important way in which the immune system regulates access to the peptide-binding groove and T cells become exposed to specific self-antigens. Differences in protease expression in the thymus and in the periphery may in part determine which specific peptide sequences comprise the peripheral repertoire for T cell recognition. It is at this stage in the intracellular pathway, after cleavage of the invariant chain, that the MHC-encoded DM molecule catalytically facilitates the exchange of peptides within the class II groove to help optimize the specificity and stability of the MHC-peptide complex.

Once this MHC-peptide complex is deposited in the outer cell membrane it becomes the target for T cell recognition via a specific TCR expressed on lymphocytes. Because the endosome environment contains internalized proteins retrieved from the extracellular environment, the class II–peptide complex often contains bound antigens that were originally derived from extracellular proteins. In this way, the class II peptide–loading pathway provides a mechanism for immune surveillance of the extracellular space. This appears to be an important feature that permits the class II molecule to bind foreign peptides, distinct from the endogenous pathway of class I–mediated presentation.

ROLE OF HLA IN TRANSPLANTATION

The development of modern clinical transplantation in the decades since the 1950s provided a major impetus for elucidation of the HLA system, as allograft survival is highest when donor and recipient are HLA-identical. Although many molecular events participate in transplantation rejection, allogeneic differences at class I and class II loci play a major role. Class I molecules can promote T cell responses in several different ways. In the cases of allografts in which the host and donor are mismatched at one or more class I loci, host T cells can be activated by classic *direct alloreactivity*, in which the antigen receptors on the host T cells react with the foreign class I molecule expressed on the allograft. In this situation, the response of any given TCR may be dominated by the allogeneic MHC molecule, the peptide bound to it, or some combination of the two. Another type of host antigraft T cell response involves the uptake and processing of donor MHC antigens by host antigen-presenting cells and the subsequent presentation of the resulting peptides by host MHC molecules. This mechanism is termed *indirect alloreactivity*.

In the case of class I molecules on allografts that are shared by the host and the donor, a host T cell response may still be triggered because of peptides that are presented by the class I molecules of the graft but not of the host. The most common basis for the existence of these endogenous antigen peptides, called *minor histocompatibility antigens*, is a genetic difference between donor and host at a non-MHC locus encoding the structural gene for the protein from which the peptide is derived. These loci are termed *minor histocompatibility loci*, and nonidentical individuals typically differ at many such loci. CD4 T cells react to analogous class II variation, both direct and indirect, and class II differences alone are sufficient to drive allograft rejection.

ASSOCIATION OF HLA ALLELES WITH SUSCEPTIBILITY TO DISEASE

It has long been postulated that infectious agents provide the driving force for the allelic diversification seen in the HLA system. An important corollary of this hypothesis is that resistance to specific pathogens may differ between individuals, based on HLA genotype. Observations of specific HLA genes associated with resistance to malaria or dengue fever, persistence of hepatitis B, and to disease progression in HIV infection are consistent with this model. For example, failure to clear persistent hepatitis B or C viral infection may reflect the inability of particular HLA molecules to present viral antigens effectively to T cells. Similarly, both protective and susceptible HLA allelic associations have been described for human papilloma virus–associated

cervical neoplasia, implicating the MHC as an influence in mediating viral clearance in this form of cancer.

Pathogen diversity is probably also the major selective pressure favoring HLA heterozygosity. The extraordinary scope of HLA allelic diversity increases the likelihood that most new pathogens will be recognized by some HLA molecules, helping to ensure immune fitness to the host. However, another consequence of diversification is that some alleles may become capable of recognition of "innocent bystander" molecules, including drugs, environmental molecules, and tissue-derived self-antigens. In a few instances, single HLA alleles display a strong selectivity for binding of a particular agent that accounts for a genetically determined response: hypersensitivity to abacavir, an antiretroviral therapeutic, is directly linked to binding of abacavir in the antigen-binding pockets of HLA-B*5701, and chronic beryllium toxicity is linked to binding of beryllium by HLA-DP molecules with a specific glutamic acid polymorphic residue on the class II beta chain. Even in the case of more complex diseases, particular HLA alleles are strongly associated with certain inappropriate immune-mediated disease states, particularly for some common autoimmune disorders (Chap. 3). By comparing allele frequencies in patients with any particular disease and in control populations, >100 such associations have been identified, some of which are listed in **Table 2-1**. The strength of genetic association is reflected in the term *relative risk*, which is a statistical odds ratio representing the risk of disease for an individual carrying a particular genetic marker compared with the risk for individuals in that population without that marker. The nomenclature shown in Table 2-1 reflects both the HLA serotype (e.g., DR3, DR4) and the HLA genotype (e.g., DRB1*0301, DRB1*0401). It very likely the class I and class II alleles themselves are the true susceptibility alleles for most of these associations. However, because of the extremely strong linkage disequilibrium between the DR and DQ loci, in some cases it has been difficult to determine the specific locus or combination of class II loci involved. In some cases, the susceptibility gene may be one of the HLA-linked genes located near the class I or class II region, but not the HLA gene itself, and in other cases the susceptibility gene may be a non-HLA gene such as TNF-α, which is nearby. Indeed, since linkage disequilibrium of some haplotypes extends across large segments of the MHC region, it is quite possible that combinations of genes may account for the particular associations of HLA haplotypes with disease. For example, on some haplotypes associated with rheumatoid arthritis, both HLA-DRB1 alleles and a particular polymorphism associated with the TNF locus may be contributory to disease risk. Other candidates for similar epistatic effects include the IKBL gene and the MICA locus, potentially in combination with classic HLA class II risk alleles.

As might be predicted from the known function of the class I and class II gene products, almost all of the diseases associated with specific HLA alleles have an immunologic component to their pathogenesis. The recent development of soluble HLA-peptide recombinant molecules as biological probes of T cell function, often in multivalent complexes referred to as "MHC tetramers," represents an opportunity to use HLA genetic associations to develop biomarkers for detection of early disease progression. However, it should be stressed that even the strong HLA associations with disease (those associations with relative risk of ≥10) implicate normal, rather than defective, alleles. Most individuals who carry these susceptibility genes do not express the associated disease; in this way, the particular HLA gene is permissive for disease but requires other environmental (e.g., the presence of specific antigens) or genetic factors for full penetrance. In each case studied, even in diseases with very strong HLA associations, the concordance of disease in monozygotic twins is higher than in HLA-identical dizygotic twins or other sibling pairs, indicating that non-HLA genes contribute to susceptibility and can significantly modify the risk attributable to HLA.

Another group of diseases is genetically linked to HLA, not because of the immunologic function of HLA alleles but rather because they are caused by autosomal dominant or recessive abnormal alleles at loci that happen to reside in or near the HLA region. Examples of these are 21-hydroxylase deficiency, hemochromatosis, and spinocerebellar ataxia.

CLASS I ASSOCIATIONS WITH DISEASE

Although the associations of human disease with particular HLA alleles or haplotypes predominantly involve the class II region, there are also several prominent disease associations with class I alleles. These include the association of Behçet's disease (Chap. 12) with HLA-B51, psoriasis vulgaris with HLA-Cw6, and, most notably, the spondyloarthritides (Chap. 10) with HLA-B27. Twenty-five HLA-B locus alleles, designated HLA-B*2701–B*2725, encode the family of B27 class I molecules. All of the subtypes share a common B pocket in the peptide-binding groove—a deep, negatively charged pocket that shows a strong preference for binding the arginine side chain. In addition, B27 is among the most negatively charged of HLA class I heavy chains, and the overall preference is for positively charged peptides. HLA-B*2705 is the predominant subtype in whites and most other non-Asian populations, and this subtype is very highly associated with ankylosing spondylitis (AS) (Chap. 10), both in its

TABLE 2-1

SIGNIFICANT HLA CLASS I AND CLASS II ASSOCIATIONS WITH DISEASE

	MARKER	GENE	STRENGTH OF ASSOCIATION
Spondyloarthropathies			
Ankylosing spondylitis	B27	B*2702, –04, –05	++++
Reactive arthritis	B27		++++
Acute anterior uveitis	B27		+++
Reactive arthritis *(Yersinia, Salmonella, Shigella, Chlamydia)*	B27		+++
Psoriatic spondylitis	B27		+++
Collagen-Vascular Diseases			
Juvenile arthritis, pauciarticular	DR8 DR5		++ ++
Rheumatoid arthritis	DR4	DRB1*0401, –04, –05	+++
Sjögren's syndrome	DR3		++
Systemic lupus erythematosus			
White Japanese	DR3 DR2		+ ++
Autoimmune Gut and Skin			
Gluten-sensitive enteropathy (celiac disease)	DQ2	DQA1*0501 DQB1*0201	+++
Chronic active hepatitis	DR3		++
Dermatitis herpetiformis	DR3		+++
Psoriasis vulgaris	Cw6		++
Pemphigus vulgaris	DR4 DQ1	DRB1*0402 DQB1*0503	+++
Bullous pemphigoid variant	DQ7	DQB1*0301	+
Autoimmune Endocrine			
Type 1 diabetes mellitus	DQ8 DR4 DR3 DR2	DQB1*0302 DRB1*0401, –04 DQB1 *0602	+++ ++ —[a]
Hyperthyroidism (Graves')	B8 DR3		+ +
Hyperthyroidism (Japanese)	B35		+
Adrenal insufficiency	DR3		++
Autoimmune Neurologic			
Myasthenia gravis	B8 DR3		+ +
Multiple sclerosis	DR2	DRB1*1501 DRB5*0101	++
Other			
Behçet's disease	B51		++
Congenital adrenal hyperplasia	B47	21·OH (Cyp21B)	+++
Narcolepsy	DR2	DQB1*0602	++++
Goodpasture's syndrome (anti-GBM)	DR2		++
Abacavir hypersensitivity	B57	B*5701	++++

[a]Strong negative association; i.e., genetic association with protection from diabetes.

idiopathic form and in association with chronic inflammatory bowel disease or psoriasis vulgaris. It is also associated with reactive arthritis (ReA) (Chap. 10), with other idiopathic forms of peripheral arthritis (undifferentiated spondyloarthropathy), and with recurrent acute anterior uveitis. B27 is found in 50–90% of individuals with these conditions, compared with a prevalence of ~7% in North American whites.

It can be concluded that the B27 molecule itself is involved in disease pathogenesis, based on strong evidence from clinical epidemiology and on the occurrence of a spondyloarthropathy-like disease in HLA-B27 transgenic rats. The association of B27 with these diseases may derive from the specificity of a particular peptide or family of peptides bound to B27 or through another mechanism that is independent of the peptide specificity of B27. In particular, HLA-B27 has been shown to form heavy chain homodimers, utilizing the cysteine residue at position 67 of the B57 α chain, in the absence of β_2-microglobulin. These homodimers are expressed on the surface of lymphocytes and monocytes from patients with AS, and receptors including KIR3DL1, KIR3DL2, and ILT4 are capable of binding to them, promoting the activation and survival of cells expressing these receptors. Alternatively, this dimerization "misfolding" of B27 may initiate an intracellular stress signalling response, called the unfolded protein response (UPR), capable of modulating immune cell function. Whether these interactions contribute to disease susceptibility or pathogenesis is currently unknown.

CLASS II DISEASE ASSOCIATIONS

As can be seen in Table 2-1, the majority of associations of HLA and disease are with class II alleles. Several diseases have complex HLA genetic associations.

Celiac disease

In the case of celiac disease, it is probable that the HLA-DQ genes are the primary basis for the disease association. HLA-DQ genes present on both the celiac-associated DR3 and DR7 haplotypes include the *DQB1*0201* gene, and further detailed studies have documented a specific class II $\alpha\beta$ dimer encoded by the *DQA1*0501* and *DQB1*0201* genes, which appears to account for most of the HLA genetic contribution to celiac disease susceptibility. This specific HLA association with celiac disease may have a straightforward explanation: peptides derived from the wheat gluten component gliaden are bound to the molecule encoded by *DQA1*0501* and *DQB1*0201* and presented to T cells. Gliaden-derived peptides that are implicated in this immune activation bind the DQ class II dimer best when the peptide contains a glutamine to glutamic acid substitution. It has been proposed that tissue transglutaminase, an enzyme present at increased levels in the intestinal cells of celiac patients, converts glutamine to glutamic acid in gliadin, creating peptides that are capable of being bound by the DQ2 molecule and presented to T cells.

Pemphigus vulgaris

In the case of pemphigus vulgaris, there are two HLA genes associated with disease, *DRB1*0402* and *DQB1*0503*. Peptides derived from desmoglien3, an epidermal autoantigen, bind to the DRB1*0402- and DQB1*0503-encoded HLA molecules, and this combination of specific peptide binding and disease-associated class II molecule is sufficient to stimulate desmoglien-specific T cells. A bullous pemphigoid clinical variant, not involving desmoglien recognition, has been found to be associated with HLA-DQB1*0301.

Juvenile arthritis

Pauciarticular juvenile arthritis (Chap. 6) is an autoimmune disease associated with genes at the DRB1 locus and also with genes at the DPB1 locus. Patients with both DPB1*0201 and a DRB1 susceptibility allele (usually DRB1*08 or -*05) have a higher relative risk than expected from the additive effect of those genes alone. In juvenile patients with rheumatoid factor–positive polyarticular disease, heterozygotes carrying both DRB1*0401 and -*0404 have a relative risk > 100, reflecting an apparent synergy in individuals inheriting both of these susceptibility genes.

Type 1 diabetes mellitus

Type 1 (autoimmune) diabetes mellitus is associated with MHC genes on more than one haplotype. The presence of both the DR3 and DR4 haplotypes in one individual confers a twentyfold increased risk for type 1 diabetes; the strongest single association is with DQB1*0302, and all haplotypes that carry a *DQB1*0302* gene are associated with type 1 diabetes, whereas related haplotypes that carry a different DQB1 gene are not. However, the relative risk associated with inheritance of this gene can be modified, depending on other HLA genes present either on the same or a second haplotype. For example, the presence of a DR2-positive haplotype containing a *DQB1*0602* gene is associated with decreased risk. This gene, *DQB1*0602*, is considered "protective" for type 1 diabetes. Even some DRB1 genes that can occur on the same haplotype as DQB1*0302 may modulate risk, so that individuals with the DR4 haplotype that contains DRB1*0403 are less susceptible to type 1 diabetes than individuals with other DR4-DQB1*0302 haplotypes.

Although the presence of a DR3 haplotype in combination with the DR4-DQB1*0302 haplotype is a very high-risk combination for diabetes susceptibility, the specific gene on the DR3 haplotype that is responsible for this synergy is not yet identified. There are some characteristic structural features of the diabetes-associated DQ molecule encoded by DQB1*0302, particularly the capability for binding peptides that have negatively charged amino acids near their C-termini. This may indicate a role for specific antigenic peptides or T cell interactions in the immune response to islet-associated proteins.

HLA and rheumatoid arthritis

The HLA genes associated with rheumatoid arthritis (RA) (Chap. 6) encode a distinctive sequence of amino acids from codons 67–74 of the DRβ molecule: RA-associated class II molecules carry the sequence LeuLeuGluGlnArgArgAlaAla or LeuLeuGluGlnLysArgAlaAla in this region, while non-RA-associated genes carry one or more differences in this region. These residues form a portion of the molecule that lies in the middle of the α-helical portion of the DRB1-encoded class II molecule, termed the *shared epitope.*

The highest risk for susceptibility to RA comes in individuals who carry both a DRB1*0401 and DRB1*0404 gene. These DR4-positive RA-associated alleles are most frequent among patients with more severe, erosive disease. Several mechanisms have been proposed that link the shared epitope to immune reactivity in RA. This portion of the class II molecule may allow preferential binding of an arthritogenic peptide, it may favor the expansion of a type of self-reactive T lymphocyte, or it may itself form part of the pMHC ligand recognized by TCR that initiates synovial tissue recognition.

MOLECULAR MECHANISMS FOR HLA-DISEASE ASSOCIATIONS

As noted earlier, HLA molecules play a key role in the selection and establishment of the antigen-specific T cell repertoire and a major role in the subsequent activation of those T cells during the initiation of an immune response. Precise genetic polymorphisms characteristic of individual alleles dictate the specificity of these interactions and thereby instruct and guide antigen-specific immune events. These same genetically determined pathways are therefore implicated in disease pathogenesis when specific HLA genes are responsible for autoimmune disease susceptibility.

The fate of developing T cells within the thymus is determined by the affinity of interaction between T cell receptor and HLA molecules bearing self-peptides, and thus the particular HLA types of each individual control the precise specificity of the T cell repertoire (Chap. 1). The primary basis for HLA-associated disease susceptibility may well lie within this thymic maturation pathway. The positive selection of potentially autoreactive T cells, based on the presence of specific HLA susceptibility genes, may establish the threshold for disease risk in a particular individual.

At the time of onset of a subsequent immune response, the primary role of the HLA molecule is to bind peptide and present it to antigen-specific T cells. The HLA complex can therefore be viewed as encoding genetic determinants of precise immunologic activation events. Antigenic peptides that bind particular HLA molecules are capable of stimulating T cell immune responses; peptides that do not bind are not presented to T cells and are not immunogenic. This genetic control of the immune response is mediated by the polymorphic sites within the HLA antigen–binding groove that interact with the bound peptides. In autoimmune and immune-mediated diseases, it is likely that specific tissue antigens that are targets for pathogenic lymphocytes are complexed with the HLA molecules encoded by specific susceptibility alleles. In autoimmune diseases with an infectious etiology, it is likely that immune responses to peptides derived from the initiating pathogen are bound and presented by particular HLA molecules to activate T lymphocytes that play a triggering or contributory role in disease pathogenesis. The concept that early events in disease initiation are triggered by specific HLA-peptide complexes offers some prospects for therapeutic intervention, since it may be possible to design compounds that interfere with the formation or function of specific HLA-peptide–T cell receptor interactions.

When considering mechanisms of HLA associations with immune response and disease, it is well to remember that just as HLA genetics are complex, so are the mechanisms likely to be heterogeneous. Immune-mediated disease is a multistep process in which one of the HLA-associated functions is to establish a repertoire of potentially reactive T cells, while another HLA-associated function is to provide the essential peptide-binding specificity for T cell recognition. For diseases with multiple HLA genetic associations, it is possible that both of these interactions occur and synergize to advance an accelerated pathway of disease.

CHAPTER 3

AUTOIMMUNITY AND AUTOIMMUNE DISEASES

Betty Diamond ■ Peter E. Lipsky

One of the central features of the immune system is the capacity to mount an inflammatory response to nonself while avoiding harm to self tissues. While recognition of self plays an important role in shaping the repertoires of immune receptors on both T and B cells, and in the clearance of apoptotic debris from tissues throughout the body, the development of potentially harmful immune responses to self-antigens is, in general, precluded. The essential feature of an autoimmune disease is that tissue injury is caused by the immunologic reaction of the organism against its own tissues. Autoimmunity, on the other hand, refers merely to the presence of antibodies or T lymphocytes that react with self-antigens and does not necessarily imply that the self-reactivity has pathogenic consequences. Autoimmunity is present in all individuals; however, autoimmune disease represents the end result of the breakdown of one or more of the basic mechanisms regulating immune tolerance.

Autoimmunity is seen in normal individuals and in higher frequency in normal older people. Polyreactive autoantibodies that recognize many host antigens are present throughout life. Expression of these antibodies may be increased following some inciting events. These are usually of the IgM heavy chain isotype and are encoded by nonmutated germline immunoglobulin variable region genes. When autoimmunity is induced by an inciting event, such as infection or tissue damage from trauma or ischemia, the autoreactivity is in general self-limited. Such autoimmunity may, however, be persistent, and then may or may not result in ensuing pathology. Even in the presence of organ pathology, it may be difficult to determine whether the damage is mediated by autoreactivity. Following an inciting event, the development of self-reactivity may be the consequence of an ongoing pathologic process, and be nonpathogenic, or may contribute to tissue inflammation and damage.

MECHANISMS OF AUTOIMMUNITY

Since Ehrlich first postulated the existence of mechanisms to prevent the generation of self-reactivity in 1900, ideas concerning the nature of this inhibition have developed in parallel with a progressive increase in understanding of the immune system. Burnet's clonal selection theory included the idea that interaction of lymphoid cells with their specific antigens during fetal or early postnatal life would lead to elimination of such "forbidden clones." This idea became untenable, however, when it was shown that autoimmune diseases could be induced in experimental animals by simple immunization procedures, that autoantigen-binding cells could be demonstrated easily in the circulation of normal individuals, and that self-limited autoimmune phenomena frequently developed following tissue damage from infection or trauma. These observations indicated that clones of cells capable of responding to autoantigens were present in the repertoire of antigen-reactive cells in normal adults and suggested that mechanisms in addition to clonal deletion were responsible for preventing their activation.

Currently, three general processes are thought to be involved in the maintenance of selective unresponsiveness to autoantigens **(Table 3-1)**: (1) sequestration of self-antigens, rendering them inaccessible to the immune system; (2) specific unresponsiveness (tolerance or anergy) of relevant T or B cells; and (3) limitation of potential reactivity by regulatory mechanisms.

Derangements of these normal processes may predispose to the development of autoimmunity **(Table 3-2)**. In general, these abnormal responses require an exogenous trigger such as bacterial or viral infection or cigarette smoking and require the presence of endogenous abnormalities in the cells of the immune system.

TABLE 3-1

MECHANISMS PREVENTING AUTOIMMUNITY

1. Sequestration of self-antigen
2. Generation and maintenance of tolerance
 a. Central deletion of autoreactive lymphocytes
 b. Peripheral anergy of autoreactive lymphocytes
 c. Receptor replacement in autoreactive lymphocytes
3. Regulatory mechanisms

Microbial superantigens, such as staphylococcal protein A and staphylococcal enterotoxins, are substances that can stimulate a broad range of T and B cells based upon specific interactions with selected families of immune receptors, irrespective of their antigen specificity. If autoantigen-reactive T and/or B cells express these receptors, autoimmunity might develop. Alternatively, molecular mimicry or cross-reactivity between a microbial product and a self-antigen might lead to activation of autoreactive lymphocytes. One of the best examples of autoreactivity and autoimmune disease resulting from molecular mimicry is rheumatic fever, in which antibodies to the M protein of streptococci cross-react with myosin, laminin, and other matrix proteins as well as neuronal antigens. Deposition of these autoantibodies in the heart initiates an inflammatory response, whereas penetration of these antibodies into the brain can result in Sydenham's chorea. Molecular mimicry between microbial proteins and host tissues has been reported in type 1 diabetes mellitus, rheumatoid arthritis, and multiple sclerosis. It is presumed that infectious agents may be able to overcome self-tolerance because they possess molecules, such as bacterial endotoxin, RNA, or DNA, that have adjuvant-like effects on the immune system that increase the immunogenicity of the microbial antigens. The adjuvants activate dendritic cells through pattern recognition receptors and stimulate the activation of previously quiescent lymphocytes that recognize both microbial and self antigen.

TABLE 3-2

MECHANISMS OF AUTOIMMUNITY

I. Exogenous
 A. Molecular mimicry
 B. Superantigenic stimulation
 C. Microbial adjuvanticity
II. Endogenous
 A. Altered antigen presentation
 1. Loss of immunologic privilege
 2. Presentation of novel or cryptic epitopes (epitope spreading)
 3. Alteration of self-antigen
 4. Enhanced function of antigen-presenting cells
 a. Co-stimulatory molecule expression
 b. Cytokine production
 B. Increased T cell help
 1. Cytokine production
 2. Co-stimulatory molecules
 C. Increased B cell function
 D. Apoptotic defects
 E. Cytokine imbalance
 F. Altered immunoregulation

Endogenous derangements of the immune system may also contribute to the loss of immunologic tolerance to self-antigens and the development of autoimmunity (Table 3-2). Some autoantigens reside in immunologically privileged sites, such as the brain or the anterior chamber of the eye. These sites are characterized by the inability of engrafted tissue to elicit immune responses. Immunologic privilege results from a number of events, including the limited entry of proteins from those sites into lymphatics, the local production of immunosuppressive cytokines such as transforming growth factor β, and the local expression of molecules such as Fas ligand that can induce apoptosis of activated T cells. Lymphoid cells remain in a state of immunologic ignorance (neither activated nor anergized) to proteins expressed uniquely in immunologically privileged sites. If the privileged site is damaged by trauma or inflammation, or if T cells are activated elsewhere, proteins expressed at this site can become the targets of immunologic assault. Such an event may occur in multiple sclerosis and sympathetic ophthalmia, in which antigens uniquely expressed in the brain and eye, respectively, become the target of activated T cells.

Alterations in antigen presentation may also contribute to autoimmunity. Peptide determinants (*epitopes*) of a self antigen that are not routinely presented to lymphocytes may be recognized as a result of altered proteolytic processing of the molecule and the ensuing presentation of novel peptides (cryptic epitopes). When B cells rather than dendritic cells present self antigen, they may also present cryptic epitopes that can activate autoreactive T cells. These cryptic epitopes will not have previously been available to effect the silencing of autoreactive lymphocytes. Furthermore, once there is immunologic recognition of one protein component of a multimolecular complex, reactivity may be induced to other components of the complex following internalization and presentation of all molecules within the complex (epitope spreading). Finally, inflammation, drug exposure, or normal senescence may cause a primary chemical alteration in proteins, resulting in the generation of immune responses that cross-react with normal self-proteins. For example, the induction and/or release of protein arginine deaminase enzymes results in the conversion of arginine residues to citrullines in a variety

of proteins, thereby altering their capacity to induce immune responses. Production of anticitrullinated protein antibodies has been observed in rheumatoid arthritis, chronic lung disease, as well as normal smokers and may contribute to organ pathology. Alterations in the availability and presentation of autoantigens may be important components of immunoreactivity in certain models of organ-specific autoimmune diseases. In addition, these factors may be relevant in understanding the pathogenesis of various drug-induced autoimmune conditions. However, the diversity of autoreactivity manifest in non-organ-specific systemic autoimmune diseases suggests that these conditions might result from a more general activation of the immune system rather than from an alteration in individual self-antigens.

Many autoimmune diseases are characterized by the presence of antibodies that react with apoptotic material. Defects in the clearance of apoptotic material have been shown to elicit autoimmunity and autoimmune disease in a number of animal models. Moreover, defects in the clearance of apoptotic material have been found in subjects with systemic lupus erythematosus (SLE). Apoptotic debris not quickly cleared by the immune system can function as endogenous ligands for a number of pattern recognition receptors on dendritic cells. Under such circumstances, there is activation of dendritic cells, and an immune response to apoptotic debris can develop. In addition, the presence of extracellular apoptotic material within germinal centers of secondary lymphoid organs may facilitate the direct activation of autoimmune B cell clones or function to select autoimmune B cell clones during immune responses.

A number of experimental models have suggested that intense stimulation of T lymphocytes can produce nonspecific signals that bypass the need for antigen-specific helper T cells and lead to polyclonal B cell activation with the formation of multiple autoantibodies. For example, antinuclear, antierythrocyte, and antilymphocyte antibodies are produced during the chronic graft-versus-host reaction. In addition, true autoimmune diseases, including autoimmune hemolytic anemia and immune complex–mediated glomerulonephritis, can also be induced in this manner. While it is clear that such diffuse activation of helper T cell activity can cause autoimmunity, nonspecific stimulation of B lymphocytes can also lead to the production of autoantibodies. Thus, the administration of polyclonal B cell activators, such as bacterial endotoxin, to normal mice leads to the production of a number of autoantibodies, including those directed to DNA and IgG (rheumatoid factor). Moreover, excess BAFF can also cause T cell–independent B cell activation and heavy chain class switching and the development of autoimmunity. SLE, for example, can be induced in mice through exuberant dendritic cell activation, a redundancy of TLR7 on the y chromosome (BXSByaa mice) or through exposure to CpG, a ligand for TLR 9. The ensuing induction of inflammatory mediators can cause a switch from production of nonpathogenic IgM autoantibodies to pathogenic IgG autoantibodies in the absence of antigen-specific T cell help.

Aberrant selection of the B or T cell repertoire at the time of antigen receptor expression can also predispose to autoimmunity. For example, B cell immunodeficiency caused by an absence of the B cell receptor–associated kinase, Bruton's tyrosine kinase, leads to X-linked agammaglobulinemia. This syndrome is characterized by reduced B cell activation, but also by diminished negative selection of autoreactive B cells probably caused by high levels of BAFF, resulting in increased autoreactivity within a diminished B cell repertoire. Likewise, negative selection of autoreactive T cells in the thymus requires expression of the autoimmune regulator (AIRE) gene that enables the expression of tissue-specific proteins in thymic medullary epithelial cells. Peptides from these proteins are expressed in the context of major histocompatibility complex (MHC) molecules and mediate the elimination of autoreactive T cells. The absence of AIRE gene expression leads to a failure of negative selection of autoreactive cells, autoantibody production, and severe inflammatory destruction of multiple organs. Individuals deficient in AIRE gene expression develop autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

Primary alterations in the activity of T and/or B cells, cytokine imbalances, or defective immunoregulatory circuits may also contribute to the emergence of autoimmunity. Diminished production of tumor necrosis factor (TNF) and interleukin (IL) 10 has been reported to be associated with the development of autoimmunity. Overproduction of type 1 interferon has also been associated with autoimmunity. Overexpression of co-stimulatory molecules on T cells similarly can lead to autoantibody production.

Autoimmunity may also result from an abnormality of immunoregulatory mechanisms. Observations made in both human autoimmune disease and animal models suggest that defects in the generation and expression of regulatory T cell activity may allow for the production of autoimmunity. It has recently been appreciated that the IPEX (immunodysregulation, polyendocrinopathy, enteropathy X-linked) syndrome results from the failure to express the FOXP3 gene, which encodes a molecule critical in the differentiation of regulatory T cells. Administration of normal regulatory T cells or factors derived from them can prevent the development of autoimmune disease in rodent models of autoimmunity. Abnormalities in the function of regulatory T cells have been noted in a number of human autoimmune

diseases, although it remains uncertain whether these are causative or are secondary abnormalities owing to inflammation. Finally, recent data indicate that B cells may also exert regulatory function, largely through the production of the cytokine IL-10. Deficiency of IL-10-producing regulatory B cells can prolong the course of an animal model of multiple sclerosis.

It should be apparent that no single mechanism can explain all the varied manifestations of autoimmunity. Furthermore, genetic evaluation has shown that a number of abnormalities often need to converge to induce an autoimmune disease. Additional factors that appear to be important determinants in the induction of autoimmunity include age, sex (many autoimmune diseases are far more common in women), genetic background, exposure to infectious agents, and environmental contacts. How all of these disparate factors affect the capacity to develop self-reactivity is currently being investigated intensively.

GENETIC CONSIDERATIONS



Evidence in humans that there are susceptibility genes for autoimmunity comes from family studies and especially from studies of twins. Studies in type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and SLE have shown that approximately 15–30% of pairs of monozygotic twins show disease concordance, compared with <5% of dizygotic twins. The occurrence of different autoimmune diseases within the same family has suggested that certain susceptibility genes may predispose to a variety of autoimmune diseases. Genetic mapping has begun to identify chromosomal regions that predispose to specific autoimmune diseases. It is notable that some genes are associated with multiple autoimmune diseases, whereas others are more specifically associated with only one autoimmune condition. The gene encoding PTPN22 is associated with multiple autoimmune diseases. Its product is a phosphatase expressed by a variety of hematopoietic cells that downregulates antigen receptor–mediated stimulation of T and B cells. A gain-of-function polymorphism of this gene is associated with type 1 diabetes mellitus, rheumatoid arthritis, and SLE in some populations. The explanation of the association of this polymorphism with autoimmune disease is uncertain, but it is likely that it diminishes antigen receptor signaling during lymphocyte development permitting escape of autoreactive clones or decreased activation-induced apoptosis of autoantigen-reactive lymphocytes in the periphery. In recent years, genomewide association studies have demonstrated a variety of other genes that are involved in human autoimmune diseases. Most genes individually confer a relatively low risk for autoimmune diseases and are found in normal individuals. No gene has been identified that is essential for autoimmune diseases. In addition to this evidence from humans, certain inbred mouse strains reproducibly develop specific spontaneous or experimentally induced autoimmune diseases, whereas others do not. These findings have led to an extensive search for genes that determine susceptibility to autoimmune disease.

The strongest consistent association for susceptibility to autoimmune disease has been found with particular alleles of the MHC. It has been suggested that the association of MHC genotype with autoimmune disease relates to differences in the ability of different allelic variations of MHC molecules to present autoantigenic peptides to autoreactive T cells. An alternative hypothesis involves the role of MHC alleles in shaping the T cell receptor repertoire during T cell ontogeny in the thymus. Additionally, specific MHC gene products may themselves be the source of peptides that can be recognized by T cells. Cross-reactivity between such MHC peptides and peptides derived from proteins produced by common microbes may trigger autoimmunity by molecular mimicry. However, MHC genotype alone does not determine the development of autoimmunity. Identical twins are far more likely to develop the same autoimmune disease than MHC-identical nontwin siblings, suggesting that genetic factors other than the MHC also affect disease susceptibility. Recent studies of the genetics of type 1 diabetes mellitus, SLE, rheumatoid arthritis, and multiple sclerosis in humans and mice have shown that there are several independently segregating disease susceptibility loci in addition to the MHC. Genes that encode molecules of the innate immune response are also involved in autoimmunity. In humans, inherited homozygous deficiency of the early proteins of the classic pathway of complement (C1q, C4, or C2) as well as genes involved in the type 1 interferon pathway are very strongly associated with the development of SLE.

IMMUNOPATHOGENIC MECHANISMS IN AUTOIMMUNE DISEASES

The mechanisms of tissue injury in autoimmune diseases can be divided into antibody-mediated and cell-mediated processes. Representative examples are listed in **Table 3-3**.

The pathogenicity of autoantibodies can be mediated through several mechanisms, including opsonization of soluble factors or cells, activation of an inflammatory cascade via the complement system, and interference with the physiologic function of soluble molecules or cells.

In autoimmune thrombocytopenic purpura, opsonization of platelets targets them for elimination by

TABLE 3-3

MECHANISMS OF TISSUE DAMAGE IN AUTOIMMUNE DISEASE

EFFECTOR	MECHANISM	TARGET	DISEASE
Autoantibody	Blocking or inactivation	α Chain of the nicotinic acetylcholine receptor	Myasthenia gravis
		Phospholipid–β_2-glycoprotein 1 complex	Antiphospholipid syndrome
		Insulin receptor	Insulin-resistant diabetes mellitus
		Intrinsic factor	Pernicious anemia
	Stimulation	TSH receptor (LATS)	Graves' disease
		Proteinase-3 (ANCA)	Granulomatosis with polyangiitis (Wegener's)
		Epidermal $cadherin_1$	Pemphigus vulgaris
		Desmoglein 3	
	Complement activation	α_3 Chain of collagen IV	Goodpasture's syndrome
	Immune-complex formation	Double-stranded DNA	Systemic lupus erythematosus
		Ig	Rheumatoid arthritis
	Opsonization	Platelet GpIIb:IIIa	Autoimmune thrombocytopenic purpura
		Rh antigens, I antigen	Autoimmune hemolytic anemia
	Antibody-dependent cellular cytotoxicity	Thyroid peroxidase, thyroglobulin	Hashimoto's thyroiditis
T cells	Cytokine production	?	Rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus
	Cellular cytotoxicity	?	Type 1 diabetes mellitus

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; LATS, long-acting thyroid stimulator; TSH, thyroid-stimulating hormone.

phagocytes. Likewise, in autoimmune hemolytic anemia, binding of immunoglobulin to red cell membranes leads to phagocytosis and lysis of the opsonized cell. Goodpasture's syndrome, a disease characterized by lung hemorrhage and severe glomerulonephritis, represents an example of antibody binding leading to local activation of complement and neutrophil accumulation and activation. The autoantibody in this disease binds to the α_3 chain of type IV collagen in the basement membrane. In SLE, activation of the complement cascade at sites of immunoglobulin deposition in renal glomeruli is considered to be a major mechanism of renal damage. Moreover, the DNA- and RNA-containing immune complexes in SLE activate TLR 9 and 7, respectively, in dendritic cells and promote a proinflammatory, immunogenic milieu conducive to amplifying the autoimmune response.

Autoantibodies can also interfere with normal physiologic functions of cells or soluble factors. Autoantibodies against hormone receptors can lead to stimulation of cells or to inhibition of cell function through interference with receptor signaling. For example, long-acting thyroid stimulators, which are autoantibodies that bind to the receptor for thyroid-stimulating hormone (TSH), are present in Graves' disease and function as agonists, causing the thyroid to respond as if there were an excess of TSH. Alternatively, antibodies to the insulin receptor can cause insulin-resistant diabetes mellitus through receptor blockade. In myasthenia gravis, autoantibodies to the acetylcholine receptor can be detected in 85–90% of patients and are responsible for muscle weakness. The exact location of the antigenic epitope, the valence and affinity of the antibody, and perhaps other characteristics determine whether activation or blockade results from antibody binding.

Antiphospholipid antibodies are associated with thromboembolic events in primary and secondary antiphospholipid syndrome and have also been associated with fetal wastage. The major antibody is directed to the phospholipid–β_2-glycoprotein I complex and appears to exert a procoagulant effect. In pemphigus vulgaris, autoantibodies bind to a component of the epidermal cell desmosome, desmoglein 3, and play a role in the induction of the disease. They exert

their pathologic effect by disrupting cell-cell junctions through stimulation of the production of epithelial proteases, leading to blister formation. Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), found in granulomatosis with polyangiitis (Wegener's), is an antibody to an intracellular antigen, the 29-kDa serine protease (proteinase-3). In vitro experiments have shown that IgG anti-c-ANCA causes cellular activation and degranulation of primed neutrophils.

It is important to note that autoantibodies of a given specificity may cause disease only in genetically susceptible hosts, as has been shown in experimental models of myasthenia gravis, SLE, rheumatic fever and rheumatoid arthritis. It is also important to be aware that once organ damage is initiated, new inflammatory cascades are initiated that can sustain and amplify the autoimmune process. Finally, some autoantibodies seem to be markers for disease but have as yet no known pathogenic potential.

AUTOIMMUNE DISEASES

Manifestations of autoimmunity are found in a large number of pathologic conditions. However, their presence does not necessarily imply that the pathologic process is an autoimmune disease. A number of attempts to establish formal criteria for the diagnosis of autoimmune diseases have been made, but none is universally accepted. One set of criteria is shown in **Table 3-4**; however, this should be viewed merely as a guide in consideration of the problem.

To classify a disease as autoimmune, it is necessary to demonstrate that the immune response to a self-antigen causes the observed pathology. Initially, the demonstration that antibodies against the affected tissue could be detected in the serum of patients suffering from various diseases was taken as evidence that these diseases had an autoimmune basis. However, such autoantibodies are also found when tissue damage is caused by trauma or infection, and the autoantibody is secondary to tissue damage. Thus, it is necessary to show that autoimmunity is pathogenic before classifying a disease as autoimmune.

If the autoantibodies are pathogenic, it may be possible to transfer disease to experimental animals by the administration of autoantibodies, with the subsequent development of pathology in the recipient similar to that seen in the patient from whom the antibodies were obtained. This has been shown, for example, in Graves' disease. Some autoimmune diseases can be transferred from mother to fetus and are observed in the newborn babies of diseased mothers. The symptoms of the disease in the newborn usually disappear as the levels of the maternal antibody decrease. An exception, however, is congenital heart block, in which damage to the developing conducting system of the heart follows in utero transfer of anti-Ro antibody from the mother to the fetus. This can result in a permanent developmental defect in the heart.

In most situations, the critical factors that determine when the development of autoimmunity results in autoimmune disease have not been delineated. The relationship of autoimmunity to the development of autoimmune disease may relate to the fine specificity of the antibodies or T cells or their specific effector capabilities. In many circumstances, a mechanistic understanding of the pathogenic potential of autoantibodies has not been established. In some autoimmune diseases, biased production of cytokines by helper T (T_H) cells may play a role in pathogenesis. In this regard, T cells can differentiate into specialized effector cells that predominantly produce interferon γ (T_H1), IL-4 (T_H2), IL-17 (T_H17) or provide help to B cells (T follicular helper, T_{FH}) (Chap. 1). T_H1 cells facilitate macrophage activation and classic cell-mediated immunity, whereas T_H2 cells are thought to have regulatory functions and are involved in the resolution of normal immune responses and also the development of responses to a variety of parasites; T_H17 cells produce a number of inflammatory cytokines, including IL-17 and IL-22, and T_{FH} cells help B cells by constitutively producing IL-21. In a number of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, and Crohn's disease, there appears to be biased differentiation of T_H1 cells, with resultant organ damage. More recently, studies suggest accentuated differentiation of T_H17 cells associated with animal models of inflammatory arthritis and also rheumatoid arthritis, whereas increased differentiation of T_{FH} cells has been associated with animal models of SLE.

TABLE 3-4

HUMAN AUTOIMMUNE DISEASE: PRESUMPTIVE EVIDENCE FOR AN IMMUNOLOGIC PATHOGENESIS

Major Criteria
1. Presence of autoantibodies or evidence of cellular reactivity to self
2. Documentation of relevant autoantibody or lymphocytic infiltrate in the pathologic lesion
3. Demonstration that relevant autoantibody or T cells can cause tissue pathology
a. Transplacental transmission
b. Adaptive transfer into animals
c. In vitro impact on cellular function
Supportive Evidence
1. Reasonable animal model
2. Beneficial effect from immunosuppressive agents
3. Association with other evidence of autoimmunity
4. No evidence of infection or other obvious cause

ORGAN-SPECIFIC VERSUS SYSTEMIC AUTOIMMUNE DISEASES

Autoimmune diseases form a spectrum, from those specifically affecting a single organ to systemic disorders with involvement of many organs (Table 3-5). Hashimoto's autoimmune thyroiditis is an example of an organ-specific autoimmune disease. In this disorder, there is a specific lesion in the thyroid associated with infiltration of mononuclear cells and damage to follicular cells. Antibody to thyroid constituents can be demonstrated in nearly all cases. Other organ- or tissue-specific autoimmune disorders include pemphigus vulgaris, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, Goodpasture's syndrome, myasthenia gravis, and sympathetic ophthalmia. One important feature of some organ-specific autoimmune diseases is the tendency for overlap, such that an individual with one specific syndrome is more likely to develop a second syndrome. For example, there is a high incidence of pernicious anemia in individuals with autoimmune thyroiditis. More striking is the tendency for individuals with an organ-specific autoimmune disease to develop multiple other manifestations of autoimmunity without the development of associated organ pathology. Thus, as many as 50% of individuals with pernicious anemia have non-cross-reacting antibodies to thyroid constituents, whereas patients with myasthenia gravis may develop antinuclear antibodies, antithyroid antibodies, rheumatoid factor, antilymphocyte antibodies, and polyclonal hypergammaglobulinemia. Part of the explanation for this may relate to the genetic elements shared by individuals with these different diseases.

Systemic autoimmune diseases differ from organ-specific diseases in that pathologic lesions are found in multiple diverse organs and tissues. The hallmark of these conditions is the demonstration of associated relevant autoimmune manifestations that are likely to be etiologic in the organ pathology. SLE represents the prototype of these disorders because of its abundance of autoimmune manifestations.

SLE is a disease of protean manifestations that characteristically involves the kidneys, joints, skin, serosal surfaces, blood vessels, and central nervous system (Chap. 4). The disease is associated with a vast array of autoantibodies whose production appears to be a part of a generalized hyperreactivity of the humoral immune system. Other features of SLE include generalized B cell hyperresponsiveness and polyclonal hypergammaglobulinemia. Current evidence suggests that both hypo- and hyperresponsiveness to antigen can lead to survival and activation of autoreactive B cells in SLE.

TABLE 3-5

SOME AUTOIMMUNE DISEASES

Organ Specific	
Graves' disease	Vitiligo
Hashimoto's thyroiditis	Autoimmune hemolytic anemia
Autoimmune polyglandular syndrome	Autoimmune thrombocytopenic purpura
Type 1 diabetes mellitus	Pernicious anemia
Insulin-resistant diabetes mellitus	Myasthenia gravis
Immune-mediated infertility	Multiple sclerosis
Autoimmune Addison's disease	Guillain-Barré syndrome
Pemphigus vulgaris	Stiff-person syndrome
Pemphigus foliaceus	Acute rheumatic fever
Dermatitis herpetiformis	Sympathetic ophthalmia
Autoimmune alopecia	Goodpasture's syndrome
Organ Nonspecific (Systemic)	
Systemic lupus erythematosus	Granulomatosis with polyangiitis (Wegener's)
Rheumatoid arthritis	Antiphospholipid syndrome
Systemic necrotizing vasculitis	Sjögren's syndrome

TREATMENT Autoimmune Diseases

Treatment of autoimmune diseases can focus on either suppressing the induction of autoimmunity, restoring normal regulatory mechanisms, or inhibiting the effector mechanisms. To eliminate autoreactive cells, immunosuppressive or ablative therapies are most commonly used. In recent years, cytokine blockade has been demonstrated to be effective in preventing immune activation in some diseases. New therapies have also been developed to target lymphoid cells more specifically, either by blocking a co-stimulatory signal needed for T or B cell activation, by blocking the migratory capacity of lymphocytes, or by eliminating the effector T cells or B cells. The efficacy of these therapies is not yet demonstrated. Newer trials are testing the possibility of using autoantigen itself to induce tolerance. One major advance in inhibiting effector mechanisms has been the introduction of cytokine blockade, targeting TNF or IL-1, that appears to limit organ damage in some diseases. Biologicals that interface with T cell activation (CTLA-4Ig) or delete B cells (anti-CD20 antibody) have also recently been approved for the treatment of rheumatoid arthritis. Therapies that prevent target organ damage or support target organ function remain an important therapeutic approach to autoimmune disease.

SECTION II

DISORDERS OF IMMUNE-MEDIATED INJURY

CHAPTER 4

SYSTEMIC LUPUS ERYTHEMATOSUS

Bevra Hannahs Hahn

DEFINITION AND PREVALENCE

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue-binding autoantibodies and immune complexes. In most patients, autoantibodies are present for a few years before the first clinical symptom appears; clinical manifestations are heterogeneous. Ninety percent of patients at diagnosis are women of childbearing years; people of all genders, ages, and ethnic groups are susceptible. Prevalence of SLE in the United States is 10 to 400 per 100,000 depending on race and gender; highest prevalence is in black women and lowest is in white men.

PATHOGENESIS AND ETIOLOGY

The proposed pathogenic mechanisms of SLE are illustrated in **Fig. 4-1**. Interactions between susceptibility genes and environmental factors result in abnormal immune responses, which vary among different patients. Those responses may include (1) activation of innate immunity (dendritic cells, monocyte/macrophages) by CpG DNA, DNA in immune complexes, viral RNA, and RNA in RNA/protein self-antigens; (2) lowered activation thresholds and abnormal activation pathways in adaptive immunity cells (T and B lymphocytes); (3) ineffective regulatory CD4+ and CD8+ T cells; and (4) reduced clearance of immune complexes and of apoptotic cells. Self-antigens (nucleosomal DNA/protein; RNA/protein in Sm, Ro, and La; phospholipids) are available for recognition by the immune system in surface blebs of apoptotic cells; thus antigens, autoantibodies, and immune complexes persist for prolonged periods of time, allowing inflammation and disease to develop. Immune cell activation is accompanied by increased secretion of proinflammatory type 1 and 2 interferons (IFNs), tumor necrosis factor α (TNF-α), interleukin (IL)-17 and B cell–maturation/survival cytokines B lymphocyte stimulator (BLyS/BAFF), and IL-10. Upregulation of genes induced by interferons is a genetic "signature" in peripheral blood cells of SLE in approximately 50% of patients. Decreased production of other cytokines also contributes to SLE: Lupus T and natural killer (NK) cells fail to produce enough IL-2 and transforming growth factor β (TGF-β) to induce and sustain regulatory CD4+ and CD8+ T cells. The result of these abnormalities is sustained production of autoantibodies (referred to in Fig. 4-1 and described in **Table 4-1**) and immune complexes; pathogenic subsets bind target tissues, with activation of complement, leading to release of cytokines, chemokines, vasoactive peptides, oxidants, and destructive enzymes. This is accompanied by influx into target tissues of T cells, monocyte/macrophages, and dendritic cells, as well as activation of resident macrophages and dendritic cells. In the setting of chronic inflammation, accumulation of growth factors and products of chronic oxidation contribute to irreversible tissue damage, including fibrosis/sclerosis, in glomeruli, arteries, brain, lungs, and other tissues.

SLE is a multigenic disease. Rare single-gene defects confer high hazard ratios (HR) for SLE (5–25), including homozygous deficiencies of early components of complement (C1q,r,s; C2; C4) and a mutation in TREX1 on the X chromosome. In most genetically susceptible individuals, normal alleles of multiple genes each contribute a small amount to abnormal immune/inflammation/tissue damage responses; if enough predisposing variations are present, disease results. Thirty to forty predisposing genes (examples listed in Fig 4-1) have been identified in recent genome-wide association studies in thousands of Northern European white patients and controls. They confer HR for SLE of 1.5–3. Such relatively weak gene polymorphisms that increase risk for SLE can be classified by their potential role in pathogenesis. Predisposing, antigen-presenting human leukocyte antigen (HLA)-molecules

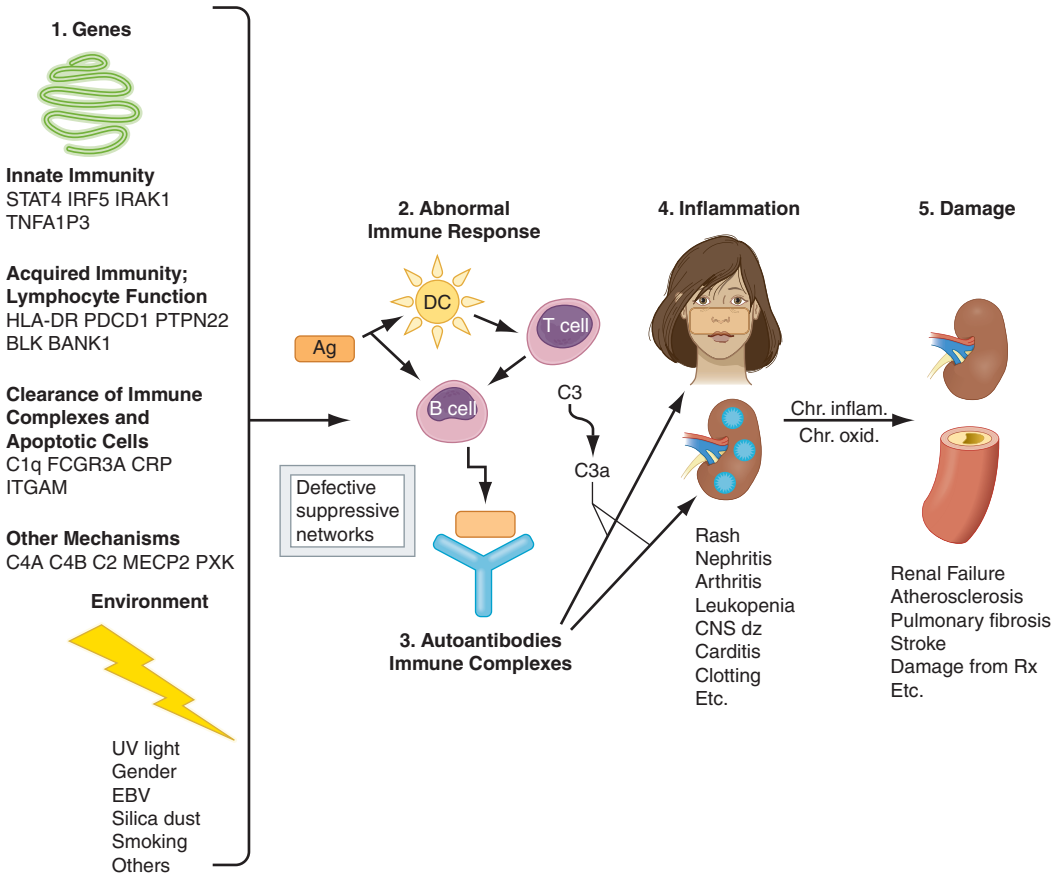


FIGURE 4-1

Pathogenesis of SLE. Genes confirmed in more than one genome-wide association analysis in Northern European whites as increasing susceptibility to SLE or lupus nephritis are listed (reviewed in Moser KL et al, Recent insights into the genetic basis of SLE. Genes Immun 2009:10:373). Gene-environment interactions result in abnormal immune responses that generate pathogenic autoantibodies and immune complexes that deposit in tissue, activate complement, cause inflammation, and over time lead to irreversible organ damage. Ag, antigen; C1q, complement system; C3, complement component; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; FcR, immunoglobulin Fc-binding receptor; IL, interleukin; MCP, monocyte chemotactic protein; PTPN, phosphotyrosine phosphatase; UV, ultraviolet.

are most commonly found, in multiple ethnic groups (HLA DRB1 *0301 and *1501, as well as multiple genes across the 120-gene region). Other genetic factors in whites include innate immunity pathway gene polymorphisms, especially associated with interferon alpha (STAT4, IRF5, IRAK1. TNFAIP3, PTPN22), genes in lymphocyte signaling pathways (PTPN22, PDCD-1, Ox40L, BANK-1, LYN, BLK), genes that affect clearance of apoptotic cells or immune complexes (C1q, FCRG IIA and IIIA, CRP, ITGAM), and genes that influence neutrophil adherence (ITGAM), and endothelial cell function (TREX-1). Some polymorphisms influence clinical manifestations; such as single nucleotide polymorphisms (SNPs) of STAT 4 that associate with severe disease, anti-DNA, nephritis, and anti-phospholipid syndrome (Chap. 5), and an allele of FCGRIIA encoding a receptor that binds immune complexes poorly and predisposes to nephritis. Some gene effects are in promoter regions (e.g., IL-10) and others are conferred by copy numbers (e.g., C4A). In addition to genome-encoded susceptibility and protective genes, the influence of certain micro (mi) RNAs on gene transcription, as well as posttranscriptional epigenetic modification of DNA, which is hypomethylated in SLE, also contribute to disease susceptibility.

Some gene polymorphisms contribute to several autoimmune diseases, such as STAT4 and CTLA4. All these gene polymorphisms/transcription/epigenetic combinations influence immune responses to the external and internal environment; when such responses are too high and/or too prolonged and/or inadequately regulated, autoimmune disease results.

Female sex is permissive for SLE with evidence for hormone effects, genes on the X chromosome,

TABLE 4-1

AUTOANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

ANTIBODY	PREVALENCE, %	ANTIGEN RECOGNIZED	CLINICAL UTILITY
Antinuclear antibodies	98	Multiple nuclear	Best screening test; repeated negative tests make SLE unlikely
Anti-dsDNA	70	DNA (double-stranded)	High titers are SLE-specific and in some patients correlate with disease activity, nephritis, vasculitis
Anti-Sm	25	Protein complexed to 6 species of nuclear U1 RNA	Specific for SLE; no definite clinical correlations; most patients also have anti-RNP; more common in blacks and Asians than whites
Anti-RNP	40	Protein complexed to U1 RNAγ	Not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites
Anti-Ro (SS-A)	30	Protein complexed to hY RNA, primarily 60 kDa and 52 kDa	Not specific for SLE; associated with sicca syndrome, predisposes to subacute cutaneous lupus, and to neonatal lupus with congenital heart block; associated with decreased risk for nephritis
Anti-La (SS-B)	10	47-kDa protein complexed to hY RNA	Usually associated with anti-Ro; associated with decreased risk for nephritis
Antihistone	70	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE
Antiphospho-lipid	50	Phospholipids, β_2 glycoprotein 1 cofactor, prothrombin	Three tests available—ELISAs for cardiolipin and β_2G1, sensitive prothrombin time (DRVVT); predisposes to clotting, fetal loss, thrombocytopenia
Antierythrocyte	60	Erythrocyte membrane	Measured as direct Coombs' test; a small proportion develops overt hemolysis
Antiplatelet	30	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia but sensitivity and specificity are not good; this is not a useful clinical test
Antineuronal (includes anti-glutamate receptor)	60	Neuronal and lymphocyte surface antigens	In some series a positive test in CSF correlates with active CNS lupus.
Antiribosomal P	20	Protein in ribosomes	In some series a positive test in serum correlates with depression or psychosis due to CNS lupus

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DRVVT, dilute Russell viper venom time; ELISA, enzyme-linked immunosorbent assay.

and epigenetic differences between genders playing a role. Females of many mammalian species make higher antibody responses than males. Women exposed to estrogen-containing oral contraceptives or hormone replacement have an increased risk of developing SLE (1.2–2-fold). Estradiol binds to receptors on T and B lymphocytes, increasing activation and survival of those cells, thus favoring prolonged immune responses. Genes on the X chromosome that influence SLE, such as TREX-1, may play a role in gender predisposition—possibly because some genes on the second X in females are not silent. People with XXY karyotype (Klinefelter's syndrome) have a significantly increased risk for SLE.

Several environmental stimuli may influence SLE (Fig. 4-1). Exposure to ultraviolet light causes flares of SLE in approximately 70% of patients, possibly by increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic. It is likely that some infections induce a normal immune response that matures to contain some T and B cells that recognize self-antigens; such cells are not appropriately regulated, and autoantibody production occurs. Most SLE patients have autoantibodies for 3 years or more before the first symptoms of disease, suggesting that regulation controls the degree of autoimmunity for years before quantities and qualities of autoantibodies

and pathogenic B and T cells cause clinical disease. Epstein-Barr virus (EBV) may be one infectious agent that can trigger SLE in susceptible individuals. Children and adults with SLE are more likely to be infected by EBV than age-, sex-, and ethnicity-matched controls. EBV contains amino acid sequences that mimic sequences on human spliceosomes (RNA/protein antigens) often recognized by autoantibodies in people with SLE. Current tobacco smoking increases risk for SLE [odds ratio (OR) 1.5]. Prolonged occupational exposure to silica (e.g., inhalation of soap powder dust) increases risk (OR 4.3) in black women. Thus, interplay between genetic susceptibility, environment, gender, and abnormal immune responses results in autoimmunity (Chap. 3).

PATHOLOGY

In SLE, biopsies of affected skin show deposition of Ig at the dermal-epidermal junction (DEJ), injury to basal keratinocytes, and inflammation dominated by T lymphocytes in the DEJ and around blood vessels and dermal appendages. Clinically unaffected skin may also show Ig deposition at the DEJ.

In renal biopsies, the pattern and severity of injury are important in diagnosis and in selecting the best therapy. Many clinical studies of lupus nephritis have used the World Health Organization (WHO) classification of lupus nephritis. However, the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) have published a newer, similar classification **(Table 4-2)** that is replacing WHO standards.

TABLE 4-2

CLASSIFICATION OF LUPUS NEPHRITIS (INTERNATIONAL SOCIETY OF NEPHROLOGY AND RENAL PATHOLOGY SOCIETY)
Class I: Minimal Mesangial Lupus Nephritis
Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
Class II: Mesangial Proliferative Lupus Nephritis
Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
Class III: Focal Lupus Nephritis
Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations. Class III (A): Active lesions—focal proliferative lupus nephritis Class III (A/C): Active and chronic lesions—focal proliferative and sclerosing lupus nephritis Class III (C): Chronic inactive lesions with glomerular scars—focal sclerosing lupus nephritis
Class IV: Diffuse Lupus Nephritis
Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than one-half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation. Class IV-S (A): Active lesions—diffuse segmental proliferative lupus nephritis Class IV-G (A): Active lesions—diffuse global proliferative lupus nephritis Class IV-S (A/C): Active and chronic lesions—diffuse segmental proliferative and sclerosing lupus nephritis Class IV-G (A/C): Active and chronic lesions—diffuse global proliferative and sclerosing lupus nephritis Class IV-S (C): Chronic inactive lesions with scars—diffuse segmental sclerosing lupus nephritis Class IV-G (C): Chronic inactive lesions with scars—diffuse global sclerosing lupus nephritis
Class V: Membranous Lupus Nephritis
Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV, in which case both will be diagnosed. Class V lupus nephritis may show advanced sclerosis.
Class VI: Advanced Sclerotic Lupus Nephritis
≥90% of glomeruli globally sclerosed without residual activity.

Note: Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

Source: JJ Weening et al: Kidney Int 65:521, 2004. Reprinted by permission from Macmillan Publishers Ltd., Copyright 2004.

An advantage of the ISN/RPS classification is the addition of "a" for active and "c" for chronic changes, giving the physician information regarding the potential reversibility of disease. All the classification systems focus on glomerular disease, although the presence of tubular interstitial and vascular disease is important to clinical outcomes. In general, class III and IV disease, as well as class V accompanied by III or IV disease, should be treated with aggressive immunosuppression if possible, because there is a high risk for end-stage renal disease (ESRD) if patients are untreated or undertreated. Treatment for lupus nephritis is not recommended in patients with class I or II disease or with extensive irreversible changes. In children, a diagnosis of SLE can be established on the basis of renal histology without meeting additional diagnostic criteria **(Table 4-3)**.

Histologic abnormalities in blood vessels may also determine therapy. Patterns of vasculitis are not specific for SLE but may indicate active disease: leukocytoclastic vasculitis is most common (Chap. 11).

Lymph node biopsies are usually performed to rule out infection or malignancies. In SLE, they show nonspecific diffuse chronic inflammation.

DIAGNOSIS

The diagnosis of SLE is based on characteristic clinical features and autoantibodies. Current criteria for classification are listed in Table 4-3, and an algorithm for diagnosis and initial therapy is shown in **Fig. 4-2**. The criteria are intended for confirming the diagnosis of SLE in patients included in studies; the author uses them in individual patients for estimating the probability that a disease is SLE. Any combination of ≥4 of 11 criteria, well documented at any time during an individual's history, makes it likely that the patient has SLE. (Specificity and sensitivity are ~95% and ~75%, respectively.) In many patients, criteria accrue over time. Antinuclear antibodies (ANA) are positive in >98% of patients during the course of disease; repeated negative tests suggest that the diagnosis is not SLE, unless other autoantibodies are present (Fig. 4-2). High-titer IgG antibodies to double-stranded DNA and antibodies to the Sm antigen are both specific for SLE and, therefore, favor the diagnosis in the presence of compatible clinical manifestations. The presence in an individual of multiple autoantibodies without clinical symptoms should not be considered diagnostic for SLE, although such persons are at increased risk.

INTERPRETATION OF CLINICAL MANIFESTATIONS

When a diagnosis of SLE is made, it is important to establish the severity and potential reversibility of the illness and to estimate the possible consequences of various therapeutic interventions. In the following sections, descriptions of some disease manifestations begin with relatively mild problems and progress to those more life-threatening.

TABLE 4-3

DIAGNOSTIC CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous circular raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Exposure to ultraviolet light causes rash
Oral ulcers	Includes oral and nasopharyngeal ulcers, observed by physician
Arthritis	Nonerosive arthritis of two or more peripheral joints, with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis documented by ECG or rub or evidence of effusion
Renal disorder	Proteinuria >0.5 g/d or ≥3+, or cellular casts
Neurologic disorder	Seizures or psychosis without other causes
Hematologic disorder	Hemolytic anemia or leukopenia (<4000/μL) or lymphopenia (<1500/μL) or thrombocytopenia(<100,000/μL) in the absence of offending drugs
Immunologic disorder	Anti-dsDNA, anti-Sm, and/or anti-phospholipid
Antinuclear antibodies	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs

If ≥4 of these criteria, well documented, are present at any time in a patient's history, the diagnosis is likely to be SLE. Specificity is ~95%; sensitivity is ~75%.

Abbreviations: ANA, antinuclear antibodies; dsDNA, double-strand DNA; ECG, electrocardiography.

Source: Criteria published by EM Tan et al: Arthritis Rheum 25:1271, 1982; update by MC Hochberg, Arthritis Rheum 40:1725, 1997.

OVERVIEW AND SYSTEMIC MANIFESTATIONS

At its onset, SLE may involve one or several organ systems; over time, additional manifestations may occur (Tables 4-3 and **4-4**). Most of the autoantibodies characteristic of each person are present at the time clinical

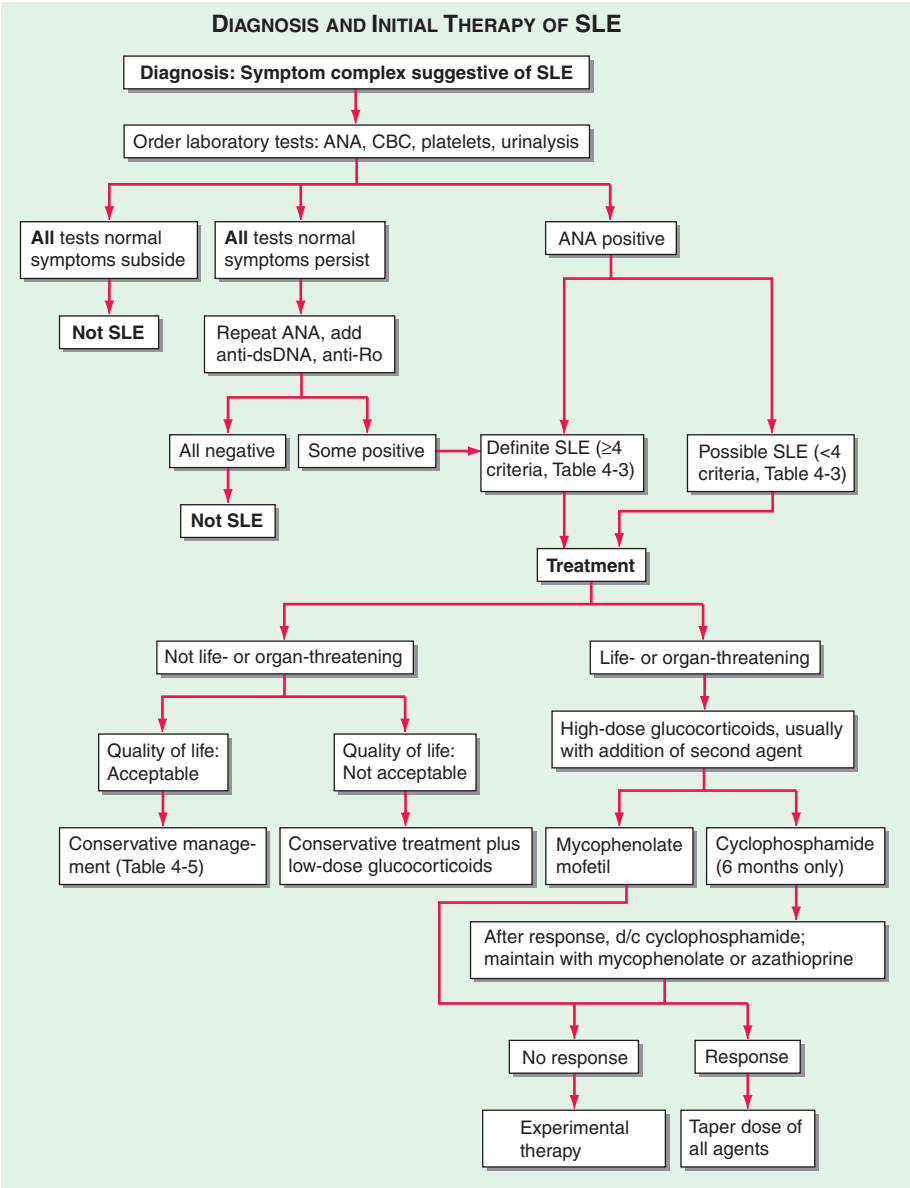


FIGURE 4-2
Algorithm for diagnosis and initial therapy of SLE. ANA, antinuclear antibodies; CBC, complete blood count.

manifestations appear (Tables 4-1 and 4-3). Severity of SLE varies from mild and intermittent to severe and fulminant. Most patients experience exacerbations interspersed with periods of relative quiescence; permanent complete remissions (absence of symptoms with no treatment) are rare. Systemic symptoms, particularly fatigue and myalgias/arthralgias, are present most of the time. Severe systemic illness requiring glucocorticoid therapy can occur with fever, prostration, weight loss, and anemia with or without other organ-targeted manifestations.

MUSCULOSKELETAL MANIFESTATIONS

Most people with SLE have intermittent polyarthritis, varying from mild to disabling, characterized by soft tissue swelling and tenderness in joints, most commonly in hands, wrists, and knees. Joint deformities (hands and feet) develop in only 10% of patients. Erosions on joint x-rays are rare; their presence suggests a non-lupus inflammatory arthropathy such as rheumatoid arthritis (Chap. 6); some experts think that erosions can occur in SLE. If pain persists in a single joint, such as knee, shoulder, or hip, a diagnosis of ischemic necrosis of bone should be considered, particularly if there are no other manifestations of active SLE. The prevalence of ischemic necrosis of bone is increased in SLE, especially in patients treated with systemic glucocorticoids. Myositis with clinical muscle weakness, elevated creatine kinase levels, positive MRI scan, and muscle necrosis and inflammation on biopsy can occur, although most patients have myalgias without frank myositis.

TABLE 4-4

CLINICAL MANIFESTATIONS OF SLE AND PREVALENCE OVER THE ENTIRE COURSE OF DISEASE*

MANIFESTATION	PREVALENCE, %	MANIFESTATION	PREVALENCE, %
Systemic: Fatigue, malaise, fever, anorexia, weight loss	95	Mono-, polyneuropathy	15
		Stroke, TIA	10
Musculoskeletal	95	Acute confusional state or movement disorder	2–5
Arthralgias/myalgias	95		
Nonerosive polyarthritis	60	Aseptic meningitis, myelopathy	<1
Hand deformities	10	**Cardiopulmonary**	60
Myopathy/myositis	25/5	Pleurisy, pericarditis, effusions	30–50
Ischemic necrosis of bone	15	Myocarditis, endocarditis	10
		Lupus pneumonitis	10
Cutaneous	80	Coronary artery disease	10
Photosensitivity	70	Interstitial fibrosis	5
Malar rash	50	Pulmonary hypertension, ARDS, hemorrhage	<5
Oral ulcers	40		
Alopecia	40	Shrinking lung syndrome	<5
Discoid rash	20	**Renal**	30–50
Vasculitis rash	20	Proteinuria >500 mg/24 h, cellular casts	30–50
Other (e.g., urticaria, subacute cutaneous lupus)	15	Nephrotic syndrome	25
		End-stage renal disease	5–10
Hematologic	85	**Gastrointestinal**	40
Anemia (chronic disease)	70	Nonspecific (nausea, mild pain, diarrhea)	30
Leukopenia (<4000/μL)	65		
Lymphopenia (<1500/μL)	50	Abnormal liver enzymes	40
Thrombocytopenia (<100,000/μL)	15	Vasculitis	5
Lymphadenopathy	15	**Thrombosis**	15
Splenomegaly	15	Venous	10
Hemolytic anemia	10	Arterial	5
Neurologic	60	**Ocular**	15
Cognitive disorder	50	Sicca syndrome	15
Mood disorder	40	Conjunctivitis, episcleritis	10
Headache	25	Vasculitis	5
Seizures	20		

*Numbers indicate percent of patients who have the manifestation at some time during the course of illness.
Abbreviations: ARDS, acute respiratory distress syndrome; TIA, transient ischemic attack.

Glucocorticoid therapies (commonly) and antimalarial therapies (rarely) can also cause muscle weakness; these adverse effects must be distinguished from active disease.

CUTANEOUS MANIFESTATIONS

Lupus dermatitis can be classified as discoid lupus erythematosus (DLE), systemic rash, subacute cutaneous lupus erythematosus (SCLE), or "other." Discoid lesions are roughly circular with slightly raised, scaly hyperpigmented erythematous rims and depigmented, atrophic centers in which all dermal appendages are permanently destroyed. Lesions can be disfiguring, particularly on the face and scalp. Treatment consists primarily of topical or locally injected glucocorticoids and systemic antimalarials. Only 5% of people with DLE have SLE (although one-half have positive ANA); however, among individuals with SLE, as many as 20% have DLE. The most common SLE rash is a photosensitive, slightly raised erythema, occasionally scaly, on the face (particularly the cheeks and nose—the "butterfly" rash), ears, chin, V region of the neck and chest, upper back, and extensor surfaces of the arms. Worsening of this rash often accompanies flare of systemic disease. SCLE consists of scaly red patches similar to psoriasis, or circular flat red-rimmed lesions. Patients with these manifestations are exquisitely photosensitive; most have antibodies to Ro (SS-A). Other SLE rashes include recurring urticaria, lichen planus–like dermatitis, bullae, and panniculitis ("lupus profundus"). Rashes can be minor or severe; they may be the major disease manifestation. Small, painful ulcerations on the oral or nasal mucosa are common in SLE; the lesions resemble aphthous ulcers.

RENAL MANIFESTATIONS

Nephritis is usually the most serious manifestation of SLE, particularly since nephritis and infection are the leading causes of mortality in the first decade of disease. Since nephritis is asymptomatic in most lupus patients, urinalysis should be ordered in any person suspected of having SLE. The classification of lupus nephritis is primarily histologic (see "Pathology," given earlier, and Table 4-2). Renal biopsy is useful in planning current and near-future therapies. Patients with dangerous proliferative forms of glomerular damage (ISN III and IV) usually have microscopic hematuria and proteinuria (>500 mg per 24 h); approximately one-half develop nephrotic syndrome, and most develop hypertension. If diffuse proliferative glomerulonephritis (DPGN) is untreated, virtually all patients develop ESRD within 2 years of diagnosis. Therefore, aggressive immunosuppression is indicated (usually systemic glucocorticoids plus a cytotoxic drug), unless 90% of glomeruli have irreversible damage (Fig. 4-2, **Table 4-5**). Blacks are more likely to develop ESRD than are whites, even with the most current therapies. Overall in the United States, ~20% of individuals with lupus DPGN die or develop ESRD within 10 years of diagnosis. Such individuals require aggressive control of SLE and of the complications of renal disease and of therapy. A small proportion of SLE patients with proteinuria (usually nephrotic) have membranous glomerular changes without proliferation on renal biopsy. Their outcome is better than for those with DPGN. Lupus nephritis tends to be an ongoing disease, with flares requiring retreatment or intensification of treatment over many years. For most people with lupus nephritis, accelerated atherosclerosis becomes important after several years of disease; attention must be given to control of systemic inflammation, blood pressure, hyperlipidemia, and hyperglycemia.

NERVOUS SYSTEM MANIFESTATIONS

There are many central nervous system (CNS) and peripheral nervous system manifestations of SLE; in some patients these are the major cause of morbidity and mortality. It is useful to approach this diagnostically by asking first whether the symptoms result from SLE or another condition (such as infection in immunosuppressed individuals). If symptoms are related to SLE, it should be determined whether they are caused by a diffuse process (requiring immunosuppression) or vascular occlusive disease (requiring anticoagulation). The most common manifestation of diffuse CNS lupus is cognitive dysfunction, including difficulties with memory and reasoning. Headaches are also common. When excruciating, they often indicate SLE flare; when milder, they are difficult to distinguish from migraine or tension headaches. Seizures of any type may be caused by lupus; treatment often requires both antiseizure and immunosuppressive therapies. Psychosis can be the dominant manifestation of SLE; it must be distinguished from glucocorticoid-induced psychosis. The latter usually occurs in the first weeks of glucocorticoid therapy, at daily doses of ≥40 mg of prednisone or equivalent; psychosis resolves over several days after glucocorticoids are decreased or stopped. Myelopathy is not rare and is often disabling; rapid immunosuppressive therapy starting with glucocorticoids is standard of care.

VASCULAR OCCLUSIONS

The prevalence of transient ischemic attacks, strokes, and myocardial infarctions is increased in patients with SLE. These vascular events are increased in, but not exclusive to, SLE patients with antibodies to phospholipids (aPL). Antiphospholipid antibodies are associated with hypercoagulability and acute thrombotic events, whereas chronic disease is associated with accelerated atherosclerosis (Chap. 5). Ischemia in the brain can be caused by focal occlusion (either noninflammatory or associated with vasculitis) or by embolization from carotid artery plaque or from fibrinous vegetations of Libman-Sacks endocarditis. Appropriate tests for aPL (discussed later) and for sources of emboli should be ordered in such patients to estimate the need for, intensity of, and duration of anti-inflammatory and/or anticoagulant therapies. In SLE, myocardial infarctions are primarily manifestations of accelerated atherosclerosis. The increased risk for vascular events is seven- to tenfold overall, and higher in women <45 years old with SLE. Characteristics associated with increased risk for atherosclerosis include older age, hypertension, dyslipidemia, dysfunctional proinflammatory high-density lipoproteins, repeated high scores for disease activity, high cumulative or daily doses of glucocorticoids, and high levels of homocysteine. When it is most likely that an event results from clotting, long-term anticoagulation is the therapy of choice. Two processes can occur at once—vasculitis plus bland vascular occlusions—in which case it is appropriate to treat with anticoagulation plus immunosuppression. Statin therapies reduce levels of low-density lipoproteins (LDL) in SLE patients; reduction of cardiac events by statins has been shown in SLE patients with renal transplants but not in other SLE cohorts to date.

PULMONARY MANIFESTATIONS

The most common pulmonary manifestation of SLE is pleuritis with or without pleural effusion. This manifestation, when mild, may respond to treatment with

TABLE 4-5

MEDICATIONS FOR THE MANAGEMENT OF SLE

MEDICATION	DOSE RANGE	DRUG INTERACTIONS	SERIOUS OR COMMON ADVERSE EFFECTS
NSAIDs, salicylates (Ecotrin[a] and St. Joseph's aspirin[a] approved by FDA for use in SLE)	Doses toward upper limit of recommended range usually required	A2R/ACE inhibitors, glucocorticoids, fluconazole, methotrexate, thiazides	NSAIDs: Higher incidence of aseptic meningitis, transaminitis, decreased renal function, vasculitis of skin; entire class, especially COX-2-specific inhibitors, may increase risk for myocardial infarction Salicylates: ototoxicity, tinnitus Both: GI events and symptoms, allergic reactions, dermatitis, dizziness, acute renal failure, edema, hypertension
Topical glucocorticoids	Mid-potency for face; mid to high potency other areas	None known	Atrophy of skin, contact dermatitis, folliculitis, hypopigmentation, infection
Topical sunscreens	SPF 15 at least; 30+ preferred	None known	Contact dermatitis
Hydroxychloroquine[a] (quinacrine can be added or substituted)	200–400 mg qd (100 mg qd)	None known	Retinal damage, agranulocytosis, aplastic anemia, ataxia, cardiomyopathy, dizziness, myopathy, ototoxicity, peripheral neuropathy, pigmentation of skin, seizures, thrombocytopenia. Use in pregnancy may be acceptable. Pregnancy category D Quinacrine usually causes diffuse yellow skin coloration
DHEA (dehydroepiandrosterone)	200 mg qd	Unclear	Acne, menstrual irregularities, high serum levels of testosterone
Methotrexate (for dermatitis, arthritis)	10–25 mg once a week, PO or SC, with folic acid; decrease dose if CrCl <60 mL/min	Acitretin, leflunomide, NSAIDs and salicylates, penicillins, probenecid, sulfonamides, trimethoprim	Anemia, bone marrow suppression, leukopenia, thrombocytopenia, hepatotoxicity, nephrotoxicity, infections, neurotoxicity, pulmonary fibrosis, pneumonitis, severe dermatitis, seizures. Teratogenic. Pregnancy category X
Glucocorticoids, oral[a] (several specific brands are approved by FDA for use in SLE)	Prednisone, prednisolone: 0.5–1 mg/kg per day for severe SLE 0.07–0.3 mg/kg per day or qod for milder disease	A2R/ACE antagonists, antiarrhythmics class III, cyclosporine, NSAIDs and salicylates, phenothiazines, phenytoins, quinolones, rifampin, risperidone, thiazides, sulfonylureas, warfarin	Infection, VZV infection, hypertension, hyperglycemia, hypokalemia, acne, allergic reactions, anxiety, aseptic necrosis of bone, cushingoid changes, CHF, fragile skin, insomnia, menstrual irregularities, mood swings, osteoporosis, psychosis
Methylprednisolone sodium succinate, IV[a] (FDA approved for lupus nephritis)	For severe disease, 1 g IV qd × 3 days	As for oral glucocorticoids	As for oral glucocorticoids (if used repeatedly); anaphylaxis
Cyclophosphamide[b,c] IV	7–25 mg/kg q month × 6; consider mesna administration with dose	Allopurinol, bone marrow suppressants, colony-stimulating factors, doxorubicin, rituximab, succinylcholine, zidovudine	Infection, VZV infection, bone marrow suppression, leukopenia, anemia, thrombocytopenia, hemorrhagic cystitis (less with IV), carcinoma of the bladder, alopecia, nausea, diarrhea, malaise, malignancy, ovarian and testicular failure. Teratogenic. Pregnancy category D
Mycophenolate mofetil[b] or mycophenolic acid	MMF: 2–3 g/d PO; max 1 g bid if CrCl <25 mL/min. MPA: 360–1080 mg bid. Caution if CrCl <25 mL/min	Acyclovir, antacids, azathioprine, bile acid–binding resins, ganciclovir, iron, salts, probenecid, oral contraceptives	Infection, leukopenia, anemia, thrombocytopenia, lymphoma, lymphoproliferative disorders, malignancy, alopecia, cough, diarrhea, fever, GI symptoms, headache, hypertension, hypercholesterolemia, hypokalemia, insomnia, peripheral edema, transaminitis, tremor, rash. Teratogenic. Pregnancy category D

(*continued*)

TABLE 4-5

MEDICATIONS FOR THE MANAGEMENT OF SLE (*CONTINUED*)

MEDICATION	DOSE RANGE	DRUG INTERACTIONS	SERIOUS OR COMMON ADVERSE EFFECTS
Azathioprine[b]	2–3 mg/kg per day PO; decrease frequency of dose if CrCl <50 mL/min	ACE inhibitors, allopurinol, bone marrow suppressants, interferons, mycophenolate mofetil, rituximab, warfarin, zidovudine	Infection, VZV infection, bone marrow suppression, leukopenia, anemia, thrombocytopenia, pancreatitis, hepatotoxicity, malignancy, alopecia, fever, flulike illness, GI symptoms. Use in pregnancy may be acceptable. Pregnancy category D
Belimumab	10 mg/kg i.v. wk 0,2,4 then monthly	IV Ig	Infusion reactions Allergy Infections probable
Rituximab (for patients resistant to above therapies)	375 mg/M2 q wk × 4 or 1 g q 2 wks × 2	IV Ig	Infection (including PML), infusion reactions, headache, arrythmias, allergic responses. Pregnancy category C

[a]Indicates medication is approved for use in SLE by the U.S. Food and Drug Administration.
[b]Indicates the medication has been used with glucocorticoids in the trials showing efficacy.
[c]See text for low dose regimen.
Abbreviations: A2R, angiotensin 2 receptor; ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SPF, sun protection factor; VZV, varicella-zoster virus.

nonsteroidal anti-inflammatory drugs (NSAIDs); when more severe, patients require a brief course of glucocorticoid therapy. Pulmonary infiltrates also occur as a manifestation of active SLE and are difficult to distinguish from infection on imaging studies. Life-threatening pulmonary manifestations include interstitial inflammation leading to fibrosis, shrinking lung syndrome, and intra-alveolar hemorrhage; all of these probably require early aggressive immunosuppressive therapy as well as supportive care.

CARDIAC MANIFESTATIONS

Pericarditis is the most frequent cardiac manifestation; it usually responds to anti-inflammatory therapy and infrequently leads to tamponade. More serious cardiac manifestations are myocarditis and fibrinous endocarditis of Libman-Sacks. The endocardial involvement can lead to valvular insufficiencies, most commonly of the mitral or aortic valves, or to embolic events. It has not been proven that glucocorticoid or other immunosuppressive therapies lead to improvement of lupus myocarditis or endocarditis, but it is usual practice to administer a trial of high-dose steroids along with appropriate supportive therapy for heart failure, arrhythmia, or embolic events. As discussed earlier, patients with SLE are at increased risk for myocardial infarction, usually due to accelerated atherosclerosis, which probably results from immune attack, chronic inflammation, and/or chronic oxidative damage to arteries.

HEMATOLOGIC MANIFESTATIONS

The most frequent hematologic manifestation of SLE is anemia, usually normochromic normocytic, reflecting chronic illness. Hemolysis can be rapid in onset and severe, requiring high-dose glucocorticoid therapy, which is effective in most patients. Leukopenia is also common and almost always consists of lymphopenia, not granulocytopenia; this rarely predisposes to infections and by itself usually does not require therapy. Thrombocytopenia may be a recurring problem. If platelet counts are >40,000/μL and abnormal bleeding is absent, therapy may not be required. High-dose glucocorticoid therapy (e.g., 1 mg/kg per day of prednisone or equivalent) is usually effective for the first few episodes of severe thrombocytopenia. Recurring or prolonged hemolytic anemia or thrombocytopenia, or disease requiring an unacceptably high dose of daily glucocorticoids, should be treated with an additional strategy (see "Treatment," later in this chapter).

GASTROINTESTINAL MANIFESTATIONS

Nausea, sometimes with vomiting and diarrhea, can be manifestations of an SLE flare, as can diffuse abdominal pain probably caused by autoimmune peritonitis and/or intestinal vasculitis. Increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are common when SLE is active. These manifestations usually improve promptly during systemic glucocorticoid therapy. Vasculitis involving the intestine may be

life-threatening; perforations, ischemia, bleeding, and sepsis are frequent complications. Aggressive immunosuppressive therapy with high-dose glucocorticoids is recommended for short-term control; evidence of recurrence is an indication for additional therapies.

OCULAR MANIFESTATIONS

Sicca syndrome (Sjögren's syndrome; Chap. 9) and nonspecific conjunctivitis are common in SLE and rarely threaten vision. In contrast, retinal vasculitis and optic neuritis are serious manifestations: blindness can develop over days to weeks. Aggressive immunosuppression is recommended, although there are no controlled trials to prove effectiveness. Complications of glucocorticoid therapy include cataracts (common) and glaucoma.

LABORATORY TESTS

Laboratory tests serve (1) to establish or rule out the diagnosis; (2) to follow the course of disease, particularly to suggest that a flare is occurring or organ damage is developing; and (3) to identify adverse effects of therapies.

TESTS FOR AUTOANTIBODIES (TABLES 4-1 AND 4-3)

Diagnostically, the most important autoantibodies to detect are ANA as the test is positive in >95% of patients, usually at the onset of symptoms. A few patients develop ANA within 1 year of symptom onset; repeated testing may thus be useful. ANA-negative lupus exists, but is rare in adults and is usually associated with other autoantibodies (anti-Ro or anti-DNA). High-titer IgG antibodies to double-stranded DNA (dsDNA) (but not to single-stranded DNA) are specific for SLE. There is no international standardized test for ANA; variability between different service laboratories is high. Enzyme-linked immunosorbent assays (ELISA) and immunofluorescent reactions of sera with the dsDNA in the flagellate *Crithidia luciliae* have ~60% sensitivity for SLE; identification of high-avidity anti-dsDNA in the Farr assay is not as sensitive but may correlate better with risk for nephritis. Titers of anti-dsDNA vary over time. In some patients, increases in quantities of anti-dsDNA herald a flare, particularly of nephritis or vasculitis, especially when associated with declining levels of C3 or C4 complement. Antibodies to Sm are also specific for SLE and assist in diagnosis; anti-Sm antibodies do not usually correlate with disease activity or clinical manifestations. aPL are not specific for SLE, but their presence fulfills one classification criterion, and they identify patients at increased risk for venous or arterial clotting, thrombocytopenia, and fetal loss. There are two widely accepted tests that measure different antibodies (anticardiolipin and the lupus anticoagulant): (1) ELISA for anticardiolipin (internationally standardized with good reproducibility) and (2) a sensitive phospholipid-based activated prothrombin time such as the dilute Russell venom viper test. Some centers also recommend measurement of antibodies to β_2 glycoprotein 1, a serum protein cofactor that is the target of most antibodies to cardiolipin and some lupus anticoagulants. The higher the titers of IgG anticardiolipin (>40 IU is considered high), and the greater the number of different aPL that are detected, the greater is the risk for a clinical episode of clotting. Quantities of aPL may vary markedly over time; repeated testing is justified if clinical manifestations of the antiphospholipid antibody syndrome (APS) appear (Chap. 5). To classify a patient as having APS, with or without SLE, by international criteria requires the presence of ≥1 clotting episode and/or repeated fetal losses plus at least two positive tests for aPL, at least 12 weeks apart; however, many patients with anti-phospholipid syndrome do not meet these stringent criteria, which are intended for inclusion of patients into studies.

An additional autoantibody test with predictive value (not used for diagnosis) detects anti-Ro, which indicates increased risk for neonatal lupus, sicca syndrome, and SCLE. Women with child-bearing potential and SLE should be screened for aPL and anti-Ro.

STANDARD TESTS FOR DIAGNOSIS

Screening tests for complete blood count, platelet count, and urinalysis may detect abnormalities that contribute to the diagnosis and influence management decisions.

TESTS FOR FOLLOWING DISEASE COURSE

It is useful to follow tests that indicate the status of organ involvement known to be present during SLE flares. These might include urinalysis for hematuria and proteinuria, hemoglobin levels, platelet counts, and serum levels of creatinine or albumin. There is great interest in identification of additional markers of disease activity. Candidates include levels of anti-DNA antibodies, several components of complement (C3 is most widely available), activated complement products (including those that bind to the C4d receptor on erythrocytes), IFN-inducible gene expression in peripheral blood cells, soluble IL-2 levels, and urinary levels of TNF-like weak inducer of apoptosis (TWEAK), neutrophil gelatinase-associated lipocalin (NGAL), or monocyte chemotactic protein 1 (MCP-1). None is uniformly agreed upon as a reliable indicator of flare or of response to therapeutic interventions. The

physician should determine for each patient whether certain laboratory test changes predict flare. If so, altering therapy in response to these changes may be advisable (30 mg of prednisone daily for 2 weeks has been shown to prevent flares in patients with rising anti-DNA plus falling complement). In addition, given the increased prevalence of atherosclerosis in SLE, it is advisable to follow the recommendations of the National Cholesterol Education Program for testing and treatment, including scoring of SLE as an independent risk factor, similar to diabetes mellitus.

TREATMENT Systemic Lupus Erythematosus

There is no cure for SLE, and complete sustained remissions are rare. Therefore, the physician should plan to induce improvement of acute flares and then maintain improvements with strategies that suppress symptoms to an acceptable level and prevent organ damage. Usually patients will endure some adverse effects of medications. Therapeutic choices depend on (1) whether disease manifestations are life-threatening or likely to cause organ damage, justifying aggressive therapies; (2) whether manifestations are potentially reversible; and (3) the best approaches to preventing complications of disease and its treatments. Therapies, doses, and adverse effects are listed in Table 4-5.

CONSERVATIVE THERAPIES FOR MANAGEMENT OF NON-LIFE-THREATENING DISEASE Among patients with fatigue, pain, and autoantibodies of SLE, but without major organ involvement, management can be directed to suppression of symptoms. Analgesics and antimalarials are mainstays. NSAIDs are useful analgesics/anti-inflammatories, particularly for arthritis/arthralgias. However, two major issues currently indicate caution in using NSAIDs. First, SLE patients compared with the general population are at increased risk for NSAID-induced aseptic meningitis, elevated serum transaminases, hypertension, and renal dysfunction. Second, all NSAIDs, particularly those that inhibit cyclooxygenase-2 specifically, may increase risk for myocardial infarction. Acetaminophen to control pain may be a good strategy, but NSAIDs are more effective in some patients. The relative hazards of NSAIDs compared with low-dose glucocorticoid therapy have not been established. Antimalarials (hydroxychloroquine, chloroquine, and quinacrine) often reduce dermatitis, arthritis, and fatigue. A randomized, placebo-controlled, prospective trial has shown that withdrawal of hydroxychloroquine results in increased numbers of disease flares. Hydroxychloroquine reduces accrual of tissue damage over time. Because of potential retinal toxicity, patients receiving antimalarials should undergo ophthalmologic examinations annually. A placebo-controlled prospective trial suggests that administration of dehydroepiandrosterone may reduce disease activity. If quality of life is inadequate in spite of these conservative measures, treatment with low doses of systemic glucocorticoids may be necessary. Dermatitis should be managed with topical sunscreens, antimalarials, and topical glucocorticoids and/or tacrolimus. Since recent data show that mycophenolate mofetil, and belimumab (added to background therapies of glucocorticoids-plus-antimalarial-plus immunosuppressive) reduce disease activity in nonrenal manifestations of SLE, it is reasonable to consider these interventions in patients with persistent disease activity despite standard therapies. Azathioprine or methotrexate may also be considered for such patients (Table 4-5).

LIFE-THREATENING SLE: PROLIFERATIVE FORMS OF LUPUS NEPHRITIS The mainstay of treatment for any inflammatory life-threatening or organ-threatening manifestations of SLE is systemic glucocorticoids (0.5–1 mg/kg per day PO or 1000 mg of methylprednisolone sodium succinate IV daily for 3 days followed by 0.5–1 mg/kg of daily prednisone or equivalent). Evidence that glucocorticoid therapy is lifesaving comes from retrospective studies from the predialysis era; survival is significantly better in people with DPGN treated with high-dose daily glucocorticoids (40–60 mg of prednisone daily for 4–6 months) versus lower doses. Currently, high doses are recommended for much shorter periods; recent trials of interventions for severe SLE employ 4–6 weeks of 0.5 to 1 mg/kg/day of prednisone or equivalent. Thereafter, doses are tapered as rapidly as the clinical situation permits, usually to a maintenance dose varying from 5–10 mg of prednisone or equivalent per day or from 10–20 mg every other day. Most patients with an episode of severe lupus require many years of maintenance therapy with low-dose glucocorticoids, which can be increased to prevent or treat disease flares. Frequent attempts to gradually reduce the glucocorticoid requirement are recommended since virtually everyone develops important adverse effects (Table 4-5). Prospective controlled trials in active lupus nephritis show that induction of improvement by administration of high doses of glucocorticoids (1000 mg of ethylprednisolone daily for 3 days) by IV routes compared with daily oral routes shortens the time to maximal improvement by a few weeks but ultimately improvements are similar. It has become standard practice to initiate therapy for active, potentially life-threatening SLE with high-dose IV glucocorticoid pulses, based on studies in lupus nephritis. This approach must be tempered by safety considerations, such as the presence of conditions adversely affected by glucocorticoids (infection, hyperglycemia, hypertension, osteoporosis, etc.).

Cytotoxic/immunosuppressive agents added to glucocorticoids are recommended to treat serious SLE. Almost all prospective controlled trials in SLE involving cytotoxic agents have been conducted in combination with glucocorticoids in patients with lupus nephritis. Therefore, the following recommendations apply to treatment of nephritis. Either cyclophosphamide (an alkylating agent) or mycophenolate mofetil (a relatively lymphocyte-specific inhibitor of inosine monophosphatase and therefore of purine synthesis) is an acceptable choice for induction of improvement in severely ill patients; azathioprine (a purine analogue and cycle-specific antimetabolite) is probably less effective but may be used if the other immunosuppressives are not tolerated or not available. In patients whose renal biopsies show ISN grade III or IV disease, early treatment with combinations of glucocorticoids and cyclophosphamide reduces progression to ESRD and improves survival; this difference can be seen after approximately 5 years of therapy. Shorter-term studies with glucocorticoids plus mycophenolate mofetil (prospective randomized trials of 6 months) show that this regimen is similar to cyclophosphamide in inducing improvement. Comparisons are complicated by effects of race, since higher proportions of blacks (and other non-Asian, non-white races) respond to mycophenolate than to cyclophosphamide, whereas similar proportions of whites and Asians respond to each drug. Regarding toxicity, diarrhea is more common with mycophenolate while herpetic infections, amenorrhea, and leukopenia are more common with cyclophosphamide; rates of severe infections and death are similar in some studies, although mycophenolate is less toxic than cyclophosphamide in others. Therapeutic responses to cyclophosphamide and mycophenolate begin 3–16 weeks after treatment is initiated, whereas glucocorticoid responses may begin within 24 h. For maintenance therapy, mycophenolate may be better than azathioprine in preventing flares and progression of lupus nephritis; either drug is acceptable and both are safer than cyclophosphamide. If cyclophosphamide is used for induction therapy, the recommended "National Institutes of Health (NIH)" dose (based on clinical trials at that institution) is 500–750 mg/m^2 intravenously, monthly for 6 months, followed by maintenance with daily oral mycophenolate or azathioprine. The incidence of ovarian failure, a common effect of cyclophosphamide therapy, can be reduced by treatment with a gonadotropin-releasing hormone agonist (e.g., Lupron 3.75 mg IM) prior to each monthly cyclophosphamide dose. Since cyclophosphamide has many adverse effects and is generally disliked by patients, alternative approaches using lower doses have been tested. European studies have shown that IV cyclophosphamide at doses of 500 mg every 2 weeks for six doses ("low dose") is as effective as the recommended higher dose given for a longer duration in the NIH regimen ("high dose"). All patients were maintained on azathioprine after the course of cyclophosphamide was completed. Ten-year follow-up has shown no differences in the high-dose and low-dose groups (death or ESRD in 9–20% in each group). The majority of the European patients were white; it is not clear that the data apply to U.S. populations. Patients with high serum creatinine levels [e.g., ≥265 μmol/L (≥3 mg/dL)] many months in duration and high chronicity scores on renal biopsy are not likely to respond to immunosuppression. In general, it may be better to induce improvement in a black or Hispanic patient with proliferative glomerulonephritis with mycophenolate (2–3 g daily) rather than with cyclophosphamide, with the option to switch if no evidence of response is detectable after 3–6 months of treatment. For whites and Asians, induction with either mycophenolate or cyclophosphamide is acceptable. Cyclophosphamide may be discontinued when it is clear that a patient is improving; the number of SLE flares is reduced by maintenance therapy with mycophenolate (1.5–2 g daily) or azathioprine (2 mg/kg/d). Both cyclophosphamide and mycophenolate are potentially teratogenic; patients should be off either medication for at least 3 months before attempting to conceive. If azathioprine is used either for induction or maintenance therapy, patients may be prescreened for homozygous deficiency of the TMPT enzyme (which is required to metabolize the 6-mercaptopurine product of azathioprine) since they are at higher risk for bone marrow suppression.

Good improvement occurs in ~80% of lupus nephritis patients receiving either cyclophosphamide or mycophenolate at 1–2 years of follow-up. However, at least 50% of these individuals have flares of nephritis over the next 5 years, and retreatment is required; such individuals are more likely to progress to ESRD. Long-term outcome of lupus nephritis to most interventions is better in whites than in blacks. Chlorambucil is an alkylating agent that can be substituted for cyclophosphamide; the risk of irreversible bone marrow suppression may be greater with this agent. Methotrexate (a folinic acid antagonist) may have a role in the treatment of arthritis and dermatitis, but probably not in nephritis or other life-threatening disease. Small controlled trials (in Asia) of leflunomide, a relatively lymphocyte-specific pyrimidine antagonist licensed for use in rheumatoid arthritis, have suggested it can suppress disease activity in some SLE patients. Cyclosporine and tacrolimus, which inhibit production of IL-2 and T lymphocyte functions, are used by some clinicians particularly for membranous lupus nephritis. Since they have potential nephrotoxicity, but little bone marrow toxicity, the author uses them

for periods of only a few months in patients with steroid-resistant cytopenias of SLE, or in steroid-resistant patients who have developed bone marrow suppression from standard cytotoxic agents.

Use of biologicals directed against B cells for active SLE is under intense study. Use of anti-CD20 (Rituximab), particularly in those patients with SLE who are resistant to the more standard combination therapies discussed earlier, is controversial. Several open trials have shown efficacy in a majority of such patients—both for nephritis and for extrarenal lupus. However, recent prospective placebo-controlled randomized trials did not show a difference between anti-CD20 and placebo when added to standard combination therapies. In contrast, recent trials of anti-BLyS (belimumab, directed against the ligand of the BLyS/BAFF receptor on B cells that promotes B cell survival and differentiation to plasmablasts) showed a small, but statistically significant, better suppression of disease activity in comparison to placebo, when added to standard combhnation therapies. The US FDA has approved belimumab for treatment of SLE: it has not been studied in active nephritis or central nervous system lupus.

It is important to note that there are few if any randomized, controlled, prospective studies of any agents in life-threatening SLE that do not include nephritis. Therefore, use of glucocorticoids plus cyclophosphamide or mycophenolate in other life-threatening conditions is based on studies in nephritis.

SPECIAL CONDITIONS IN SLE THAT MAY REQUIRE ADDITIONAL OR DIFFERENT THERAPIES

Crescentic Lupus Nephritis The presence of cellular or fibrotic crescents in glomeruli with proliferative glomerulonephritis (INS-IVG)] indicates a worse prognosis than in patients without this feature. There are few large prospective controlled trials showing efficacy of cyclophosphamide, mycophenolate, or cyclosporine in such cases. Most authorities currently recommend that cyclophosphamide in the NIH-recommended high dose or high doses of mycophenolate are the induction therapies of choice, in addition to glucocorticoids.

Membranous Lupus Nephritis Most SLE patients with membranous (INS-V) nephritis also have proliferative changes and should be treated for proliferative disease; however, some have pure membranous changes. Treatment for this group is less well defined; recent prospective controlled trials suggest that alternate-day glucocorticoids plus cyclophosphamide or mycophenolate or cyclosporine are all effective in the majority of patients in reducing proteinuria; whether they preserve renal function over the lonf term is more controversial.

Pregnancy and Lupus Fertility rates for men and women with SLE are probably normal. However, rate of fetal loss is increased (approximately two- to threefold) in women with SLE. Fetal demise is higher in mothers with high disease activity, antiphospholipid antibodies, and/or active nephritis. Suppression of disease activity can be achieved by administration of systemic glucocorticoids. A placental enzyme, 11-β-dehydrogenase 2, deactivates glucocorticoids; it is more effective in deactivating prednisone and prednisolone than the fluorinated glucocorticoids dexamethasone and betamethasone. Glucocorticoids are listed by the FDA as pregnancy category A (no evidence of teratogenicity in human studies); cyclosporine, tacrolimus, and rituximab are listed as category C (may be teratogenic in animals but no good evidence in humans); azathioprine, hydroxychloroquine, mycophenolate mofetil, and cyclophosphamide are category D (there is evidence of teratogenicity in humans. but benefits might outweigh risks in certain situations); and methotrexate is category X (risks outweigh benefits). Therefore, active SLE in pregnant women should be controlled with prednisone/prednisolone at the lowest effective doses for the shortest time required. Adverse effects of prenatal glucocorticoid exposure (primarily betamethasone) on offspring may include low birth weight, developmental abnormalities in the CNS, and predilection toward adult metabolic syndrome. It is likely that each of these glucocorticoids and immunosuppressive medications get into breast milk, at least in low levels; patients should consider not breast-feeding if they need therapy for SLE. In SLE patients with aPL (on at least two occasions) and prior fetal losses, treatment with heparin (usually low-molecular-weight) plus low-dose aspirin has been shown in prospective controlled trials to increase significantly the proportion of live births; however, a recent prospective trial showed no differences in fetal outcomes in women taking aspirin compared to those on aspirin plus low-molecular-weight heparin. An additional potential problem for the fetus is the presence of antibodies to Ro, sometimes associated with neonatal lupus consisting of rash and congenital heart block. The latter can be life-threatening; therefore, the presence of anti-Ro requires vigilant monitoring of fetal heart rates with prompt intervention (delivery if possible) if distress occurs. To date, treatments of mother to reverse established heart block in the fetus, newborn, or infant (other than insertion of a pacemaker) have not been successful. Women with SLE usually tolerate pregnancy without disease flares. However, a small proportion develops severe flares requiring aggressive glucocorticoid therapy or early delivery. Poor maternal outcomes are highest in women with active nephritis or irreversible organ damage in kidneys, brain, or heart.

Lupus and Antiphospholipid Antibody Syndrome (Chap. 5) Patients with SLE who have venous or arterial clotting, and/or repeated fetal losses, and at least two positive tests for aPL have APS and should be managed with long-term anticoagulation. A target international normalized ratio (INR) of 2–2.5 is recommended for patients with one episode of venous clotting; an INR of 3–3.5 is recommended for patients with recurring clots or arterial clotting, particularly in the central nervous system. Recommendations are based on both retrospective and prospective studies of posttreatment clotting events and adverse effects from anticoagulation.

Microvascular Thrombotic Crisis (Thrombotic Thrombocytopenic Purpura, Hemolytic-Uremic Syndrome) This syndrome of hemolysis, thrombocytopenia, and microvascular thrombosis in kidneys, brain, and other tissues carries a high mortality rate and occurs most commonly in young individuals with lupus nephritis. The most useful laboratory tests are identification of schistocytes on peripheral blood smears, elevated serum levels of lactate dehydrogenase, and antibodies to ADAMS13. Plasma exchange or extensive plasmapheresis is usually life-saving; most authorities recommend concomitant glucocorticoid therapy; there is no evidence that cytotoxic drugs are effective.

Lupus Dermatitis Patients with any form of lupus dermatitis should minimize exposure to ultraviolet light, employing appropriate clothing and sunscreens with a sun protection factor of at least 15. Topical glucocorticoids and antimalarials (such as hydroxychloroquine) are effective in reducing lesion severity in most patients and are relatively safe. Systemic treatment with retinoic acid is a useful strategy in patients with inadequate improvement on topical glucocorticoids and antimalarials; adverse effects are potentially severe (particularly fetal abnormalities), and there are stringent reporting requirements for its use in the United States. Extensive, pruritic, bullous, or ulcerating dermatitides usually improve promptly after institution of systemic glucocorticoids; tapering may be accompanied by flare of lesions, thus necessitating use of a second medication such as hydroxychloroquine, retinoids, or cytotoxic medications such as methotrexate or azathioprine. In therapy-resistant lupus dermatitis there are reports of success with topical tacrolimus (caution must be exerted because of the possible increased risk for malignancies) or with systemic dapsone or thalidomide (the extreme danger of fetal deformities from thalidomide requires permission from and supervision by the supplier).

PREVENTIVE THERAPIES Prevention of complications of SLE and its therapy include providing appropriate vaccinations (the administration of influenza and pneumococcal vaccines has been studied in patients with SLE; flare rates are similar to those receiving placebo) and suppressing recurrent urinary tract infections. In addition, strategies to prevent osteoporosis should be initiated in most patients likely to require long-term glucocorticoid therapy and/or with other predisposing factors. Control of hypertension and appropriate prevention strategies for atherosclerosis, including monitoring and treatment of dyslipidemias, management of hyperglycemia, and obesity, are recommended.

EXPERIMENTAL THERAPIES Studies of highly targeted experimental therapies for SLE are in progress. They include targeting (1) activated B lymphocytes with anti-BLyS, or TACI-Ig; (2) inhibition of IFNα; (3) inhibition of B/T cell second signal co-activation with CTLA-Ig; and (4) inhibition of innate immune activation via TLR7 or TLR7 and 9, and induction of regulatory T cells with peptides from immunoglobulins or autoantigens. A few studies have employed vigorous untargeted immunosuppression with high-dose cyclophosphamide plus anti–T cell strategies, with rescue by transplantation of autologous hematopoietic stem cells for the treatment of severe and refractory SLE. One U.S. report showed an estimated mortality rate over 5 years of 15% and sustained remission in 50%. It is hoped that the next edition of this text will recommend more effective and less toxic approaches to treatment of SLE based on some of these strategies.

PATIENT OUTCOMES, PROGNOSIS, AND SURVIVAL

Survival in patients with SLE in the United States, Canada, Europe, and China is approximately 95% at 5 years, 90% at 10 years, and 78% at 20 years. In the United States, African Americans and Hispanic Americans with a mestizo heritage have a worse prognosis than whites, whereas Africans in Africa and Hispanic Americans with a Puerto Rican origin do not. The relative importance of gene mixtures and environmental differences accounting for ethnic differences is not known. Poor prognosis (~50% mortality in 10 years) in most series is associated with (at the time of diagnosis) high serum creatinine levels [>124 μmol/L (>1.4 mg/dL)], hypertension, nephrotic syndrome (24-h urine protein excretion >2.6 g), anemia [hemoglobin <124 g/L (<12.4 g/dL)], hypoalbuminemia, hypocomplementemia, aPL, male sex, and ethnicity (African American, Hispanic with mestizo heritage). Data regarding outcomes in SLE patients with renal transplants

show mixed results: some series have a twofold increase in graft rejection compared to patients with other causes of ESRD, whereas others show no differences. Overall patient survival is comparable (85% at 2 years). Lupus nephritis occurs in approximately 10% of transplanted kidneys. Disability in patients with SLE is common due primarily to chronic fatigue, arthritis, and pain, as well as renal disease. As many as 25% of patients may experience remissions, sometimes for a few years, but these are rarely permanent. The leading causes of death in the first decade of disease are systemic disease activity, renal failure, and infections; subsequently, thromboembolic events become increasingly frequent causes of mortality.

DRUG-INDUCED LUPUS

This is a syndrome of positive ANA associated with symptoms such as fever, malaise, arthritis or intense arthralgias/myalgias, serositis, and/or rash. The syndrome appears during therapy with certain medications and biologic agents, occurs predominantly in whites, has less female predilection than SLE, rarely involves kidneys or brain, is rarely associated with anti-dsDNA, is commonly associated with antibodies to histones, and usually resolves over several weeks after discontinuation of the offending medication. The list of substances that can induce lupus-like disease is long. Among the most frequent are the antiarrhythmics procainamide, disopyramide, and propafenone; the antihypertensive hydralazine; several angiotensin-converting enzyme inhibitors and beta blockers; the antithyroid propylthiouracil; the antipsychotics chlorpromazine and lithium; the anticonvulsants carbamazepine and phenytoin; the antibiotics isoniazid, minocycline, and macrodantin; the antirheumatic sulfasalazine; the diuretic hydrochlorothiazide; the antihyperlipidemics lovastatin and simvastatin; and interferons and TNF inhibitors. ANA usually appears before symptoms; however, many of the medications mentioned earlier induce ANA in patients who never develop symptoms of drug-induced lupus. It is appropriate to test for ANA at the first hint of relevant symptoms and to use test results to help decide whether to withdraw the suspect agent.

CHAPTER 5

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

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DEFINITION

Antiphospholipid antibody syndrome (APS) is an autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity in the presence of autoantibodies against phospholipid (PL)-binding plasma proteins, mainly a plasma apolipoprotein known as β2 glycoprotein I (β2GPI) and prothrombin **(Table 5-1)**. Another group of antibodies termed *lupus anticoagulant* (LA) prolong clotting times in vitro; this prolongation is not corrected by adding normal plasma to the detection system. APS may occur alone (primary), or in association with any other autoimmune disease (secondary). Catastrophic APS (CAPS) is defined as a rapidly progressive thromboembolic disease involving simultaneously three or more organs, organ systems, or tissues leading to corresponding functional defects.

TABLE 5-1

CLASSIFICATION AND NOMENCLATURE OF ANTIPHOSPHOLIPID ANTIBODIES

- Antibodies against cardiolipin (aCL), a negatively charged phospholipid, detected by enzyme-linked immunosorbent assay (ELISA)
- Antibodies against β2GPI, (anti-β2GPI) detected by ELISA in the absence of PL.
- LA detected by clotting assays. LA constitutes a heterogeneous group of antibodies directed also against PL binding proteins, mainly β2GPI and prothrombin. LA antibodies induce elongation in vitro of the following clotting times:

Activated partial thromboplastin time (aPTT), kaolin clotting time (KCT), dilute Russel viper venom test (dRVVT)

- Antibodies against phospholipids/cholesterol complexes detected as biologic false-positive serologic test for syphilis (BFP-STS) and Venereal Disease Research Laboratory Test (VDRL)

EPIDEMIOLOGY

Anti-PL (aPL)-binding plasma protein antibodies occur in 1–5% of general population. Their prevalence increases with age; however, it is questionable whether they induce thrombotic events in elderly individuals. One-third of patients with systemic lupus erythematosus (SLE) (Chap. 4) possess these antibodies while their prevalence in other autoimmune connective tissue disorders such as systemic sclerosis (scleroderma), Sjögren's syndrome, dermatomyositis, rheumatoid arthritis, and early undifferentiated connective tissue disease, ranges from 6% to 15%. One-third of aPL positive individuals experience thrombotic events or pregnancy morbidity.

PATHOGENESIS

The trigger for the induction of antibodies to PL-binding proteins is not known. Preceding infections, however, have been proposed as the initiating event. These antibodies are pathogenic since anti-β2GPI/β2GPI complexes inactivate natural anticoagulants such as protein C, activate cells involved in the coagulation cascade to a prothrombotic phenotype, activate complement, and inhibit syncytium-trophoblast differentiation. Activated protein C (APC) binds the pro-coagulant factors Va and VIIIa and inactivates them. Anti-β2GPI/β2GPI complexes inhibit the APC activity in vivo by competing with the components of the APC/Va/VIIIa complexes for binding to a number of PL-binding sites, or by disrupting these complexes. Domain V of β2GPI can interact with apolipoprotein E receptor 2′ (apoER2′) and/or with the GPIbα subunit of the GPIb/IX/V receptor of platelets. Furthermore platelet factor 4 (PF4) tetramers dimerize β2GPI and the resulting complexes are recognized by anti-β2GPI antibodies, eventually activating the p38 mitogen-activated protein (p38 MAP) kinase phosphorylation, and leading

to thromboxane B_2 (TXB_2) production in vitro. In fact, increased levels of 11-dehydro-TXB_2, have been found in the urine of patients with APS. Anti-β2GPI antibodies activate nuclear factor kappa B (NF-κB) in monocytes and endothelial cells by interacting with surface receptors not yet identified, leading to the secretion of pro-inflammatory cytokines, such as interleukins -1, -6, and -8; the expression of adhesion molecules such as intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin; inhibition of cell-surface plasminogen activation; and the expressions of tissue factor, changing the phenotype of these cells to a prothrombotic form. As shown in mouse models, anti-β2GPI antibodies induce fetal injury through complement activation, since C4-deficient mice were protected from fetal injury.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Clinical manifestations represent mainly a direct or indirect expression of venous or arterial thrombosis and/or pregnancy morbidity (Table 5-2). Clinical features associated with venous thrombosis are superficial and deep vein thrombosis, cerebral venous thrombosis, signs and symptoms of intracranial hypertension, retinal vein thrombosis, pulmonary emboli, pulmonary arterial hypertension, and Budd-Chiari syndrome. Livedo reticularis consists of a mottled reticular vascular pattern that appears as a lace-like, purplish discoloration of the skin. It is probably caused by swelling of the venules owing to obstruction of capillaries by thrombi. This clinical manifestation correlates with vascular lesions such as those in the central nervous system as well as aseptic bone necrosis. Arterial thrombosis is manifested as migraines, cognitive dysfunction, transient ischemic attacks, stroke, myocardial infarction, arterial thrombosis of upper and lower extremities, ischemic leg ulcers, digital gangrene, avascular necrosis of bone, retinal artery occlusion leading to painless monocular loss of vision (amaurosis fugax), renal artery stenosis, and glomerular lesions, as well as infarcts of spleen, pancreas, and adrenals. Libman-Sacks endocarditis consists of very small vegetations, histologically characterized by organized platelet-fibrin microthrombi surrounded by growing fibroblasts and macrophages. Glomerular lesions are manifested with hypertension, mildly elevated serum creatinine levels, proteinuria, and mild hematuria. Histologically, these lesions are characterized in an acute phase by thrombotic microangiopathy involving glomerular capillaries, and in a chronic phase with fibrous intima hyperplasia, fibrous and/or fibrocellular occlusions of arterioles and focal cortical atrophy (Table 5-2). Premature atherosclerosis has been recognized as a rare feature of APS.

TABLE 5-2

CLINICAL FEATURES OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME

MANIFESTATION	%
Venous Thrombosis and Related Consequences	
Deep vein thrombosis	39
Livedo reticularis	24
Pulmonary embolism	14
Superficial thrombophlebitis	12
Thrombosis in various other sites	11
Arterial Thrombosis and Related Consequences	
Stroke	20
Cardiac valve thickening/dysfunction and/or Libman-Sacks vegetations	14
Transient ischemic attack	11
Myocardial ischemia (infarction or angina) and coronary bypass thrombosis	10
Leg ulcers and/or digital gangrene	9
Arterial thrombosis in the extremities	7
Retinal artery thrombosis/amaurosis fugax	7
Ischemia of visceral organs or avascular necrosis of bone	6
Multi-infarct dementia	3
Neurologic Manifestations of Uncertain Etiology	
Migraine	20
Epilepsy	7
Chorea	1
Cerebellar ataxia	1
Transverse myelopathy	0.5
Renal Manifestations Due to Various Reasons (Renal Artery/Renal Vein/Glomerular Thrombosis, Fibrous Intima Hyperplasia)	3
Osteoarticular Manifestations	
Arthralgia	39
Arthritis	27
Obstetric Manifestations (Referred to the Number of Pregnancies)	
Preeclampsia	10
Eclampsia	4
Fetal Manifestations (Referred to the Number of Pregnancies)	
Early fetal loss (<10 weeks)	35
Late fetal loss (≥10 weeks)	17
Premature birth among the live births	11
Hematologic Manifestations	
Thrombocytopenia	30
Autoimmune hemolytic anemia	10

Source: Adapted from R Cervera et al: Arthritis Rheum 46:1019, 2002.

Coombs-positive hemolytic anemia and thrombocytopenia are laboratory findings associated with APS. Discontinuation of therapy, major surgery, infection, and trauma may trigger CAPS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of APS should be seriously considered in cases of thrombosis, cerebral vascular accidents in individuals younger than 55 years of age, or pregnancy morbidity in the presence of livedo reticularis or thrombocytopenia. In these cases aPL antibodies should be measured. The presence of at least one clinical and one laboratory criterion ensures the diagnosis even in the presence of other causes of thrombophilia. Clinical criteria include: (1) vascular thrombosis defined as one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ; and (2) pregnancy morbidity, defined as (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation; or (b) one or more premature births of a morphologically normal neonate before the thirty-fourth week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation. Laboratory criteria include (1) LA, (2) anticardiolipin (aCL) and/or (3) anti-β2GPI antibodies, at intermediate or high titers on two occasions, 12 weeks apart.

Differential diagnosis is based on the exclusion of other inherited or acquired causes of thrombophilia, Coombs positive hemolytic anemia, and thrombocytopenia. Livedo reticularis with or without a painful ulceration on the lower extremities also may be a manifestation of disorders affecting (1) the vascular wall such as polyarteritis nodosa, SLE, cryoglobulinemia, and lymphomas; or (2) the vascular lumen, such as myeloproliferative disorders, atherosclerosis, hypercholesterolemia, or other causes of thrombophilia.

TREATMENT Antiphospholipid Antibody Syndrome

After the first thrombotic event, APS patients should be placed on warfarin for life aiming to achieve an international normalized ratio (INR) ranging from 2.5 to 3.5, alone or in combination with 80 mg of aspirin daily. Pregnancy morbidity is prevented by a combination of heparin with aspirin 80 mg daily. Intravenous immunoglobulin (IVIg) 400 mg/kg qd for 5 days may also prevent abortions, while glucocorticoids are ineffective. Evidence-based treatment of patients with aPL in the absence of any clinical event is not available; however, aspirin 80 mg daily protects patients with SLE positive for aPL antibodies from developing thrombotic events.

Some patients with APS and patients with CAPS have recurrent thrombotic events despite appropriate anticoagulation. In these cases IVIg 400 mg/kg qd for 5 days or anti-CD20 monoclonal antibody 375 mg/m^2 per week for 4 weeks may be of benefit. Patients with CAPS, who are treated in the intensive care unit, are unable to receive warfarin; in this situation therapeutic doses of low-molecular-weight heparin should be administered. In cases of heparin-induced thrombocytopenia and thrombosis syndrome, inhibitors of phospholipid-bound activated factor X (FXa), such as fondaparinux 7.5 mg SC daily or rivaroxaban 10 mg PO daily are effective. The above drugs are administered by fixed doses and do not require close monitoring; their safety during the first trimester of pregnancy has not been clearly established.

CHAPTER 6

RHEUMATOID ARTHRITIS

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Because it is a systemic disease, RA may result in a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities.

Insights gained by a wealth of basic and clinical research over the past two decades have revolutionized the contemporary paradigms for the diagnosis and management of RA. Serum antibodies to cyclic citrullinated peptides (anti-CCPs) are now recognized to be a valuable biomarker of diagnostic and prognostic significance. Advances in ultrasound and magnetic resonance imaging have improved our ability to detect joint inflammation and destruction in RA. The science of RA has taken a major leap forward with the identification of new disease-related genes and further deciphering of the molecular pathways of disease pathogenesis. The relative importance of these different mechanisms has been highlighted by the observed benefits of the new class of highly targeted biologic therapies. Despite these gains, incomplete understanding of the initiating pathogenic pathways of RA remains a sizable barrier to its cure and prevention.

The last two decades have witnessed a remarkable improvement in the outcomes of RA. The historic descriptions of crippling arthritis are currently encountered much less frequently. Much of this progress can be traced to the expanded therapeutic armamentarium and the adoption of early treatment intervention. The shift in treatment strategy dictates a new mind-set for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for prompt diagnosis and initiation of therapy. Only then will patients achieve their best outcomes.

CLINICAL FEATURES

The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. The presenting symptoms of RA typically result from inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting more than 1 hour and easing with physical activity. The earliest involved joints are typically the small joints of the hands and feet. The initial pattern of joint involvement may be monoarticular, oligoarticular (≤4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with an inflammatory arthritis will present with too few affected joints and other characteristic features to be classified as having RA—so-called undifferentiated inflammatory arthritis. Those with an undifferentiated arthritis, who are most likely to be diagnosed later with RA, have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or anti-CCP antibodies, and have higher scores for physical disability.

Once the disease process of RA is established, the wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints stand out as the most frequently involved joints **(Fig. 6-1)**. Distal interphalangeal (DIP) joint involvement may occur in RA, but it usually is a manifestation of coexistent osteoarthritis. Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength, and "trigger" fingers. Progressive destruction of the joints and soft tissues may lead to chronic, irreversible deformities. Ulnar deviation results from subluxation of the MCP joints, with subluxation of the proximal phalanx to the volar side of the hand. Hyperextension of the PIP joint with flexion of the DIP joint ("swan-neck deformity"), flexion of the PIP joint with hyperextension of the DIP joint ("boutonnière deformity"), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint ("Z-line deformity") also



FIGURE 6-1
Metacarpophalangeal and proximal interphalangeal joint swelling in rheumatoid arthritis. (*Courtesy of the American College of Rheumatology Image Bank.*)

may result from damage to the tendons, joint capsule, and other soft tissues in these small joints. Inflammation about the ulnar styloid and tenosynovitis of the extensor carpi ulnaris may cause subluxation of the distal ulna, resulting in a "piano-key movement" of the ulnar styloid. While metatarsophalangeal joint (MTP) involvement is a feature of early disease in the feet, the ankle and midtarsal regions are usually affected later in the course of disease and often predispose to pes planovalgus ("flat feet"). Large joints, including the knees and shoulders, are often affected in established disease, although these joints may remain asymptomatic for many years after onset.

Atlantoaxial involvement of the cervical spine is clinically noteworthy because of its potential to cause compressive myelopathy and neurologic dysfunction. Neurologic manifestations are rarely a presenting sign or symptom of atlantoaxial disease, but they may evolve over time with progressive instability of C1 on C2. The prevalence of atlantoaxial subluxation has been declining in recent years, and occurs now in less than 10% of patients. Unlike the spondyloarthritides (Chap. 10), RA does not affect the thoracic and lumbar spine except in very unusual circumstances. Radiographic abnormalities of the temporomandibular joint occur commonly in patients with RA, but they are rarely associated with significant symptoms or functional impairment.

Extraarticular manifestations may develop during the clinical course of RA, even prior to the onset of arthritis **(Fig. 6-2)**. Patients most likely to develop extraarticular disease have a history of smoking, early onset of significant physical disability, and test positive for serum RF. Subcutaneous nodules, secondary Sjögren's syndrome, pulmonary nodules, and anemia are among the most frequently observed extraarticular manifestations. Recent studies have shown a decrease in the incidence and severity of at least some extraarticular manifestations, particularly Felty's syndrome and vasculitis.

The most common systemic and extraarticular features of RA are described in more detail in the sections below.

CONSTITUTIONAL

These signs and symptoms include weight loss, fever, fatigue, malaise, depression, and in the most severe cases, cachexia; they generally reflect a high degree of inflammation and may even precede the onset of joint symptoms. In general, the presence of a fever of >38.3°C (101°F) at any time during the clinical course should raise suspicion of systemic vasculitis (discussed later) or infection.

NODULES

Subcutaneous nodules occur in 30–40% of patients and more commonly in those with the highest levels of disease activity, the disease-related shared epitope (discussed later), a positive test for serum RF, and radiographic evidence of joint erosions. When palpated, the nodules are generally firm; nontender; and adherent to periosteum, tendons, or bursae; developing in areas of the skeleton subject to repeated trauma or irritation such as the forearm, sacral prominences, and the Achilles tendon. They may also occur in the lungs, pleura, pericardium, and peritoneum. Nodules are typically benign, although they can be associated with infection, ulceration, and gangrene.

SJÖGREN'S SYNDROME

Secondary Sjögren's syndrome (Chap. 9) is defined by the presence of either keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth) in association with another connective tissue disease, such as RA. Approximately 10% of patients with RA have secondary Sjögren's syndrome.

PULMONARY

Pleural disease, the most common pulmonary manifestation of RA, may produce pleuritic chest pain and dyspnea, as well as a pleural friction rub and effusion. Pleural effusions tend to be exudative with increased numbers of monocytes and neutrophils. Interstitial lung disease (ILD) may also occur in patients with RA and is heralded by symptoms of dry cough and progressive shortness of breath. Diagnosis is readily made by high-resolution chest CT scan. Pulmonary function

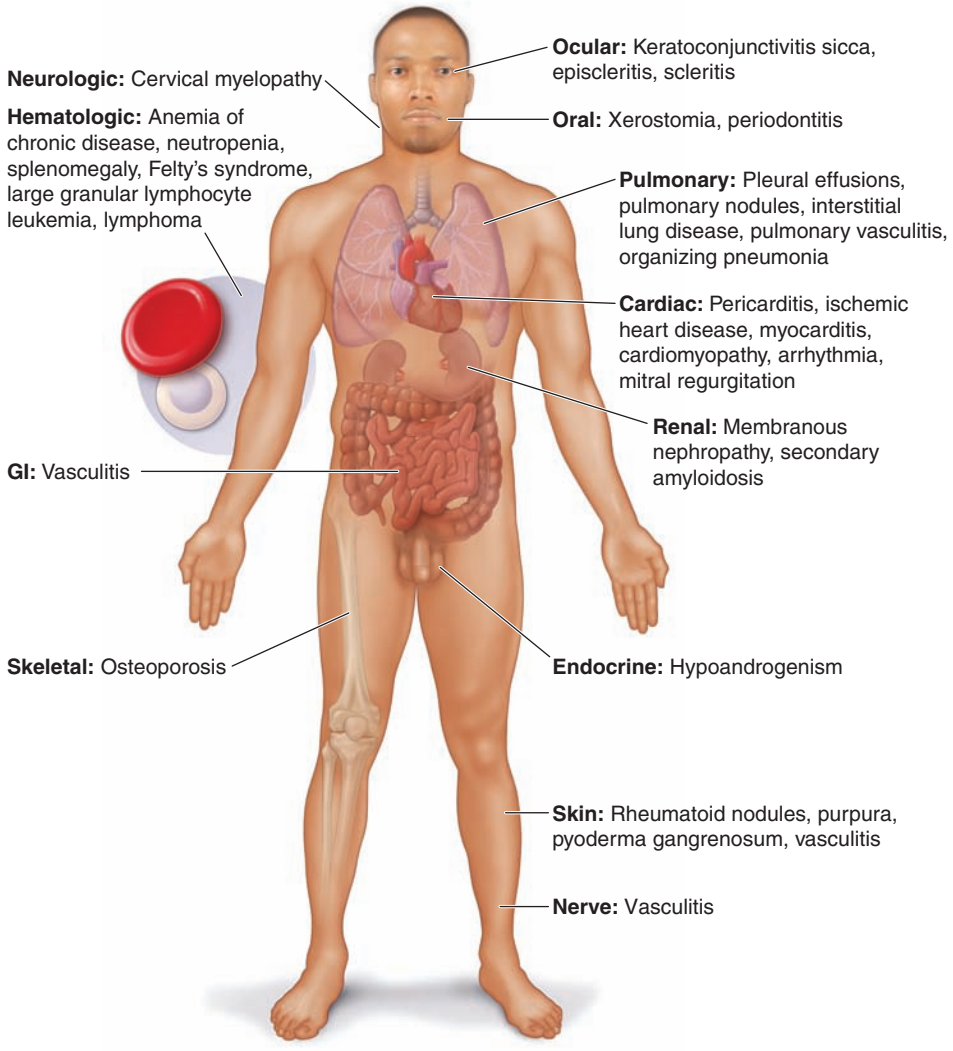


FIGURE 6-2
Extraarticular manifestations of rheumatoid arthritis.

testing shows a restrictive pattern (e.g., reduced total lung capacity) with a reduced diffusing capacity for carbon monoxide (DLCO). The presence of ILD confers a poor prognosis. The prognosis is not quite as poor as that of idiopathic pulmonary fibrosis (e.g., usual interstitial pneumonitis) because ILD secondary to RA responds more favorably than idiopathic ILD to immunosuppressive therapy. Pulmonary nodules may be solitary or multiple. Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure. Other less common pulmonary findings include respiratory bronchiolitis and bronchiectasis.

CARDIAC

The most frequent site of cardiac involvement in RA is the pericardium. However, clinical manifestations of pericarditis occur in less than 10% of patients with RA despite the fact that pericardial involvement may be detected in nearly one-half of the these patients by echocardiogram or autopsy studies. Cardiomyopathy, another clinically important manifestation of RA, may result from necrotizing or granulomatous myocarditis, coronary artery disease, or diastolic dysfunction. This involvement too may be subclinical and only identified by echocardiography or cardiac MRI. Rarely, the heart muscle may contain rheumatoid nodules or be infiltrated with amyloid. Mitral regurgitation is the most common valvular abnormality in RA, occurring at a higher frequency than the general population.

VASCULITIS

Rheumatoid vasculitis (Chap. 11) is seen most commonly in patients with long-standing disease, a positive test for serum RF, and hypocomplementemia; the overall incidence is quite rare, occurring in no more than 1% of cases. The cutaneous signs vary and include petechiae,

purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, painful lower extremity ulcerations. Vasculitic ulcers, which may be difficult to distinguish from those caused by venous insufficiency, may be treated successfully with immunosuppressive agents (requiring cytotoxic treatment in severe cases) as well as skin grafting. Sensorimotor polyneuropathies, such as mononeuritis multiplex, may occur in association with systemic rheumatoid vasculitis.

HEMATOLOGIC

A normochromic, normocytic anemia often develops in patients with RA and is the most common hematologic abnormality. The degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Platelet counts may also be elevated in RA as an acute-phase reactant. Immune-mediated thrombocytopenia is rare in this disease.

Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA and is seen in less than 1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease. It typically occurs in white patients in the late stages of severe RA. T cell large granular lymphocyte leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA. T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly. As opposed to Felty's syndrome, T-LGL may develop early in the course of RA. Leukopenia apart from these disorders is uncommon and most often due to drug therapy.

LYMPHOMA

Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population. The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma. The risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

ASSOCIATED CONDITIONS

In addition to extraarticular manifestations, several conditions associated with RA contribute to disease morbidity and mortality rates. They are worthy of mention because they affect chronic disease management.

Cardiovascular disease

The most common cause of death in patients with RA is cardiovascular disease. The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking. Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population. The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease in this population.

Osteoporosis

Osteoporosis is more common in patients with RA than an age- and sex-matched population, with prevalence rates of 20–30%. The inflammatory milieu of the joint probably spills over into the rest of the body and promotes generalized bone loss by activating osteoclasts. Chronic use of glucocorticoids and disability-related immobility also contributes to osteoporosis. Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

Hypoandrogenism

Men and postmenopausal women with RA have lower mean serum testosterone, luteinizing hormone (LH) and dehydroepiandrosterone (DHEA) levels than control populations. It has thus been hypothesized that hypoandrogenism may play a role in the pathogenesis of RA or arise as a consequence of the chronic inflammatory response. In fact, some studies suggest that higher testosterone levels offer some protection from RA in younger males. The idea that the low serum testosterone levels associated with RA arise from the chronic inflammatory state comes from observations that clinical improvement following successful treatment correlates with an increase in serum testosterone levels. From a clinical perspective, it is important to realize that patients receiving chronic glucocorticoid therapy may develop hypoandrogenism owing to inhibition of LH and follicle-stimulating hormone (FSH) secretion from the pituitary gland. Since low testosterone levels may lead to osteoporosis, men with serum testosterone levels below the physiologic range should be considered for androgen replacement therapy.

EPIDEMIOLOGY

RA affects approximately 0.5–1% of the adult population worldwide. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. The incidence and

European ancestry:
HLA-DRB1:
*0401
*0404
*0301
***0101**

PTPN22: European
STAT 4: North American
TNFAIP3: North American
TRAFI/CF: North American
CTLA-4: European

Asian ancestry:
HLA-DRB1:
*0401 (East Asian)
*0405
*0901 (Japanese, Malaysian, Korean)

PADI4
CD244

Other:
CD40

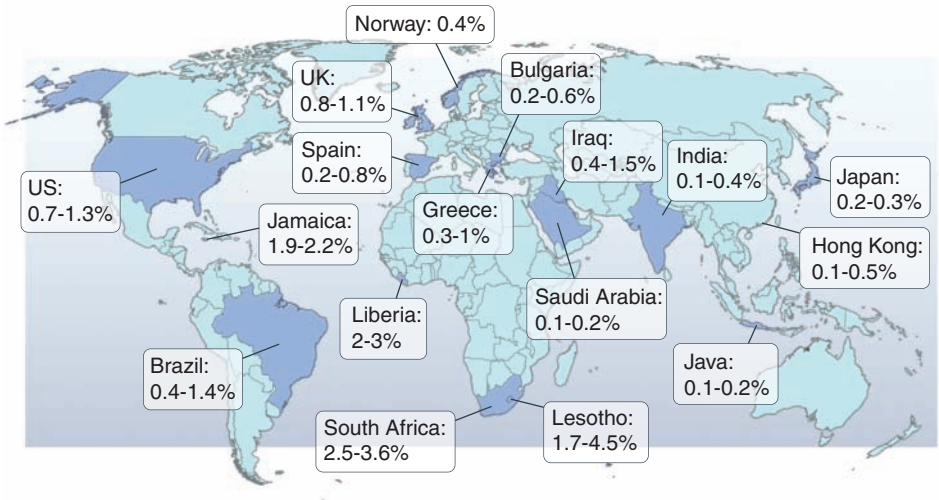


FIGURE 6-3

Global prevalence rates of rheumatoid arthritis (RA) with genetic associations. Listed are the major genetic alleles associated with RA. While human leukocyte antigen (HLA)-DRB1 mutations are found globally, some alleles have been associated with RA in only certain ethnic groups.

prevalence of RA varies based on geographic location, both globally and among certain ethnic groups within a country (Fig. 6-3). For example, the Native American Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates in some studies of nearly 7%. In contrast, many population studies from Africa and Asia show lower prevalence rates for RA in the range of 0.2–0.4%.

Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2–3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1. Given this preponderance of females, various theories have been proposed to explain the possible role of estrogen in disease pathogenesis. Most of the theories center on the role of estrogens in enhancing the immune response. For example, some experimental studies have shown that estrogen can stimulate production of tumor necrosis factor α (TNF-α), a major cytokine in the pathogenesis of RA.

GENETIC CONSIDERATIONS

It has been recognized for over 30 years that genetic factors contribute to the occurrence of RA as well as to its severity. The likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2–10 times greater than in the general population. There remains, however, some uncertainty in the extent to which genetics plays a role in the causative mechanisms of RA. While twin studies imply that genetic factors may explain up to 60% of the occurrence of RA, the more commonly stated estimate falls in the range of 10–25%. The estimate of genetic influence may vary across studies due to gene–environment interactions.

The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC). It has been estimated that one-third of the genetic risk for RA resides within this locus. Most, but probably not all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β-chain molecule. The disease-associated HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β-chain, termed the *shared epitope (SE)*. Carriership of the SE alleles is associated with production of anti-CCP antibodies and worse disease outcomes. Some of these HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, *0404, *1001, and *0901). In Greece, for example, where RA tends to be milder than in western European countries, RA susceptibility has been associated with the *0101 SE allele. By comparison, the *0401 or *0404 alleles are found in approximately 50–70% of Northern Europeans and are the predominant risk alleles in this group. The most common disease

susceptibility SE alleles in Asians, namely the Japanese, Koreans, and Chinese, are *0405 and *0901. Lastly, disease susceptibility of Native American populations such as the Pima and Tlingit Indians, where the prevalence of RA can be as high as 7%, is associated with the SE allele *1042. The risk of RA conferred by these SE alleles is less in African and Hispanic Americans than in individuals of European ancestry.

Genome-wide association studies (GWAS) have made possible the identification of several non-MHC-related genes that contribute to RA susceptibility. GWAS are based on the detection of single-nucleotide polymorphisms (SNPs), which allow for examination of the genetic architecture of complex diseases such as RA. There are approximately 10 million common SNPs within a human genome consisting of 3 billion base pairs. As a rule, GWAS identify only common variants, namely, those with a frequency of more than 5% in the general population.

Overall, several themes have emerged from GWAS in RA. First, several of the non-MHC loci identified as risk alleles for RA have only a modest effect on risk; they also contribute to the risk for developing other autoimmune diseases, such as Type 1 diabetes mellitus, systemic lupus erythematosus, and multiple sclerosis. Second, most of the associations are described in patients with anti-CCP antibody-positive disease. Third, risk alleles vary among ethnic groups. Fourth, the risk loci mostly reside in genes encoding proteins involved in the regulation of the immune response, such as the signaling pathway for the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). However, the risk alleles identified by GWAS only account at present for approximately 5% of the genetic risk, suggesting that rare variants or other classes of DNA variants, such as variants in copy number, may be yet found that significantly contribute to the overall risk model.

Among the best examples of the non-MHC genes contributing to the risk of RA is the gene encoding protein tyrosine phosphatase non-receptor 22 (PTPN22). This gene varies in frequency among patients from different parts of Europe (e.g., 3–10%), but is absent in patients of East Asian ancestry. PTPN22 encodes lymphoid tyrosine phosphatase, a protein that regulates T and B cell function. Inheritance of the risk allele for PTPN22 produces a gain-of-function in the protein that is hypothesized to result in the abnormal selection of autoreactive T and B cells. In RA, carriage of the variant PTPN22 appears to be associated exclusively with anti-CCP-positive disease. The peptidyl arginine deiminase type IV (PADI4) gene is another risk allele that encodes an enzyme involved in the conversion of arginine to citrulline and is postulated to play a role in the development of antibodies to citrullinated antigens. A polymorphism in PADI4 has been only associated with RA in Asian populations. Other SNPs associated with RA have been found in the genes for signal transducer and activator of transcription 4 (STAT4), CD244 (natural killer cell receptor 2B4), Fc receptor-like 3 (FCLR3), tumor necrosis factor (TNF) alpha-induced protein 3 (TNF-AIP3), and TNF receptor-associated factor 1 (TRAF1). These genes encode proteins with various roles in B and T cell signaling.

ENVIRONMENTAL FACTORS

In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA. The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5–3.5. A twin who smokes will have a significantly higher risk for RA than his or her monozygotic co-twin, theoretically with the same genetic risk, who does not smoke. Interestingly, the risk from smoking is almost exclusively related to RF- and anti-CCP antibody-positive disease.

Researchers began to aggressively seek an infectious etiology for RA after the discovery in 1931 that sera from patients with this disease could agglutinate strains of streptococci. Certain viruses such as Epstein-Barr virus (EBV) have garnered the most interest over the past 30 years given their ubiquity, ability to persist for many years in the host, and frequent association with arthritic complaints. For example, titers of IgG antibodies against EBV antigens in the peripheral blood and saliva are significantly higher in patients with RA than the general population. EBV DNA has also been found in synovial fluid and synovial cells of RA patients. Blood and synovial fluid analyses have also suggested a possible link with mycoplasma and parvovirus B19 infection. Since the evidence for these links is largely circumstantial, it has not been possible to directly implicate infection as a causative factor in RA.

PATHOLOGY

RA affects the synovial tissue and underlying cartilage and bone. The synovial membrane, which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue. In joints, it faces the bone and cartilage, bridging the opposing bony surfaces and inserting at periosteal regions close to the articular cartilage. It consists primarily of two cell types—type A synoviocytes (macrophage-derived) and type B synoviocytes (fibroblast-derived). The synovial fibroblasts are the most abundant and produce the structural

components of joints, including collagen, fibronectin, and laminin, as well as other extracellular constituents of the synovial matrix. The sublining layer consists of blood vessels and a sparse population of mononuclear cells within a loose network of connective tissue. Synovial fluid, an ultrafiltrate of blood, diffuses through the subsynovial lining tissue across the synovial membrane and into the joint cavity. Its main constituents are hyaluronan and lubricin. Hyaluronan is a glycosaminoglycan that contributes to the viscous nature of synovial fluid, which along with lubricin, lubricates the surface of the articular cartilage.

The pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. Chronic inflammation leads to synovial lining hyperplasia and the formation of pannus, a thickened cellular membrane of granulation–reactive fibrovascular tissue that invades the underlying cartilage and bone. Cadherin-11, the chief organizing molecule of the synovial membrane, confers the invasive nature of the fibroblast-like synoviocytes, the prevailing cell type of the pannus. The inflammatory infiltrate is made up of no less than 6 cell types: T cells, B cells, plasma cells, dendritic cells, mast cells, and a few granulocytes. The T cells comprise 30–50% of the infiltrate, with the other cells accounting for the remainder. The topographical organization of these cells is complex and may vary among individuals with RA. Most often, the lymphocytes are diffusely organized among the tissue resident cells; however, in some cases, the B cells, T cells, and dendritic cells may form higher levels of organization, such as lymphoid follicles and germinal center–like structures. Growth factors secreted by synovial fibroblasts and macrophages promote the formation of new blood vessels in the synovial sublining that supply the increasing demands for oxygenation and nutrition required by the infiltrating leukocytes and expanding synovial tissue.

The structural damage to the mineralized cartilage and subchondral bone is mediated by the osteoclast. Osteoclasts are multinucleated giant cells that can be identified by their expression of CD68, tartrate-resistant acid phosphatase, cathepsin K, and the calcitonin receptor. They appear at the pannus-bone interface where they eventually form resorption lacunae. These lesions typically localize where the synovial membrane inserts into the periosteal surface at the edges of bones close to the rim of articular cartilage and at the attachment sites of ligaments and tendon sheaths. This process most likely explains why bone erosions usually develop at the radial sites of the MCP joints juxtaposed to the insertion sites of the tendons, collateral ligaments, and synovial membrane. Another form of bone loss is periarticular osteopenia that occurs in joints with active inflammation. It is associated with substantial thinning of the bony trabeculae along the metaphyses of bones, and likely results from inflammation of the bone marrow cavity. These lesions can be visualized on MRI scans, where they appear as signal alterations in the bone marrow adjacent to inflamed joints. Their signal characteristics show they are water-rich with a low fat content, and consistent with highly vascularized inflammatory tissue. These bone marrow lesions are often the forerunner of bone erosions.

The cortical bone layer that separates the bone marrow from the invading pannus is relatively thin and susceptible to penetration by the inflamed synovium. The bone marrow lesions seen on MRI scans are associated with an endosteal bone response characterized by the accumulation of osteoblasts and deposition of osteoid. Thus, in recent years, the concept of joint pathology in RA has been extended to include the bone marrow cavity. Finally, a third form of bone loss is generalized osteoporosis, which results in the thinning of trabecular bone throughout the body.

Articular cartilage is an avascular tissue comprised of a specialized matrix of collagens, proteoglycans, and other proteins. It is organized in four distinct regions (superficial, middle, deep, and calcified cartilage zones)—chondrocytes constitute the unique cellular component in these layers. Originally, cartilage was considered to be an inert tissue, but it is now known to be a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which in turn, alter the balance between cartilage anabolism and catabolism. In RA, the initial areas of cartilage degradation are juxtaposed to the synovial pannus. The cartilage matrix is characterized by a generalized loss of proteoglycan, most evident in the superficial zones adjacent to the synovial fluid. Degradation of cartilage may also take place in the perichondrocytic zone and in regions adjacent to the subchondral bone.

PATHOGENESIS

The pathogenic mechanisms of synovial inflammation are likely to result from a complex interplay of genetic, environmental, and immunologic factors that produces dysregulation of the immune system and a breakdown in self-tolerance **(Fig. 6-4)**. Precisely what triggers these initiating events and what genetic and environmental factors disrupt the immune system remain a mystery. However, a detailed molecular picture is emerging of the mechanisms underlying the chronic inflammatory response and the destruction of the articular cartilage and bone.

In RA, the earliest detectable preclinical stage is a breakdown in self-tolerance. This idea is supported by the finding that autoantibodies, such as RF and anti-CCP antibodies, may be found in sera from patients

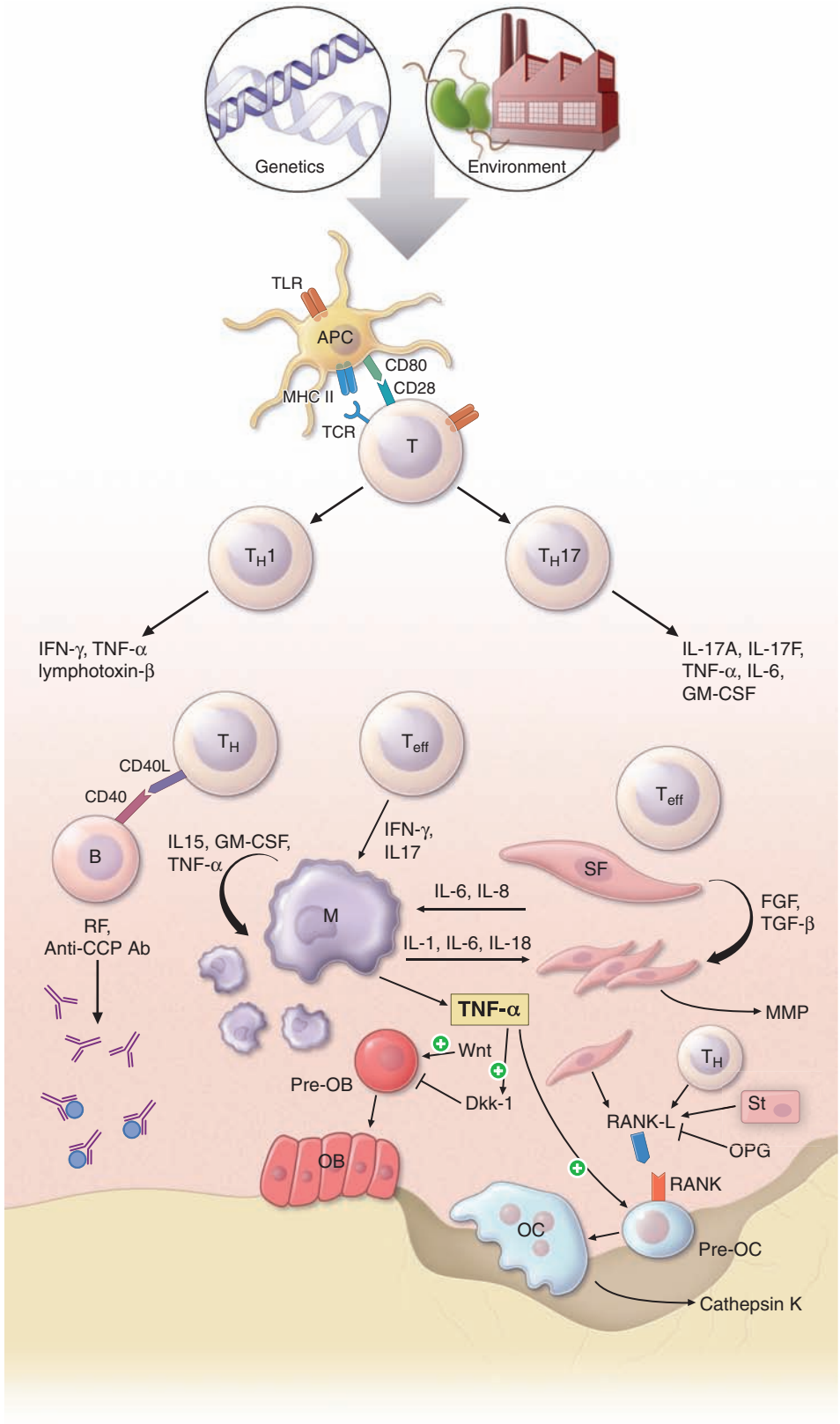


FIGURE 6-4

Pathophysiologic mechanisms of inflammation and joint destruction. Genetic predisposition along with environmental factors may trigger the development of rheumatoid arthritis (RA), with subsequent synovial T cell activation. CD4+ T cells become activated by antigenpresenting cells (APCs) through interactions between the T cell receptor and class II major histocompatibility complex (MHC)-peptide antigen (signal 1) with co-stimulation through the CD28-CD80/86 pathway, as well as other pathways (signal 2). In theory, ligands binding Toll-like receptors (TLRs) may further stimulate activation

long before clinical disease. However, the antigenic targets of anti-CCP antibodies and RF are not restricted to the joint, and their role in disease pathogenesis remains speculative. Anti-CCP antibodies are directed against deiminated peptides, which result from posttranslational modification by the enzyme PADI4. They recognize citrulline-containing regions of several different matrix proteins, including filaggrin, keratin, fibrinogen, and vimentin. Other autoantibodies have been found in a minority of patients with RA, but they also occur in the setting of other types of arthritis. They bind to a diverse array of autoantigens, including type II collagen, human cartilage gp-39, aggrecan, calpastatin, BiP (immunoglobulin binding protein), and glucose-6-phosphate isomerase.

In theory, environmental stimulants may synergize with other factors to bring about inflammation in RA. People who smoke display higher citrullination of proteins in bronchoalveolar fluid than those who do not smoke. Thus, it has been speculated that long-term exposure to tobacco smoke might induce citrullination of cellular proteins in the lungs and enhance the expression of a neoepitope capable of inducing self-reactivity. Exposure to silicone dust and mineral oil, which has adjuvant effects, has also been linked to an increased risk for anti-CCP antibody-positive RA.

How might microbes or their products be involved in the initiating events of RA? The immune system is alerted to the presence of microbial infections through Toll-like receptors (TLRs). There are 10 TLRs in humans that recognize a variety of microbial products, including bacterial cell-surface lipopolysaccharides and heat- shock proteins (TLR4), lipoproteins (TLR2), double-strand RNA viruses (TLR3), and unmethylated CpG DNA from bacteria (TLR9). TLR2, -3, and -4 are abundantly expressed by synovial fibroblasts in early RA, and when bound by their ligands upregulate production of proinflammatory cytokines. Although such events could amplify inflammatory pathways in RA, a specific role for TLRs in disease pathogenesis has not been elucidated.

The pathogenesis of RA is built upon the concept that self-reactive T cells drive the chronic inflammatory response. In theory, self-reactive T cells might arise in RA from abnormal central (thymic) selection due to defects in DNA repair leading to an imbalance of T cell death and life, or defects in the cell signaling apparatus lowering the threshold for T cell activation. Similarly, abnormal selection of the T cell repertoire in the periphery might lead to a breakdown in T cell tolerance. The support for these theories comes mainly from studies of arthritis in mouse models. It has not been shown that patients with RA have abnormal thymic selection of T cells or defective apoptotic pathways regulating cell death. At least some antigen stimulation inside the joint seems likely, owing to the fact that T cells in the synovium express a cell-surface phenotype indicating prior antigen exposure and show evidence of clonal expansion. Of interest, peripheral blood T cells from patients with RA have been shown to display a fingerprint of premature aging that mostly affects inexperienced naïve T cells. In these studies, the most glaring findings have been the loss of telomeric sequences and a decrease in the thymic output of new T cells. While intriguing, it is not clear how generalized T cell abnormalities might provoke a systemic disease dominated by synovitis.

There is substantial evidence supporting a role for CD4+ T cells in the pathogenesis of RA. First, the co-receptor CD4 on the surface of T cells binds to

of APCs inside the joint. Synovial CD4+ T cells differentiate into T_H1 and T_H17 cells, each with their distinctive cytokine profile. CD4+ T_H cells in turn activate B cells, some of which are destined to differentiate into autoantibody-producing plasma cells. Immune complexes, possibly comprised of rheumatoid factors (RFs) and anti–cyclic citrullinated peptides (CCP) antibodies, may form inside the joint, activating the complement pathway and amplifying inflammation. T effector cells stimulate synovial macrophages (M) and fibroblasts (SF) to secrete proinflammatory mediators, among which is tumor necrosis factor α (TNF-α). TNF-α upregulates adhesion molecules on endothelial cells, promoting leukocyte influx into the joint. It also stimulates the production of other inflammatory mediators, such as interleukin 1 (IL-1), IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). TNF-α has a critically important function in regulating the balance between bone destruction and formation. It upregulates the expression of dickkopf-1 (DKK-1), which can then internalize Wnt receptors on osteoblast precursors. Wnt is a soluble mediator that promotes osteoblastogenesis and bone formation. In RA, bone formation is inhibited through the Wnt pathway, presumably due to the action of elevated levels of DKK-1. In addition to inhibiting bone formation, TNF-α stimulates osteoclastogenesis. However, it is not sufficient by itself to induce the differentiation of osteoclast precursors (Pre-OC) into activated osteoclasts capable of eroding bone. Osteoclast differentiation requires the presence of macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κB (RANK) ligand, which binds to RANK on the surface of Pre-OC. Inside the joint, RANKL is mainly derived from stromal cells, synovial fibroblasts, and T cells. Osteoprotegerin (OPG) acts as a decoy receptor for RANKL, thereby inhibiting osteoclastogenesis and bone loss. FGF, fibroblast growth factor; IFN, interferon; TGF, transforming growth factor.

invariant sites on MHC class II molecules, stabilizing the MHC-peptide–T cell receptor complex during T cell activation. Since the SE on MHC class II molecules is a risk factor for RA, it may be speculated that CD4+ T cell activation plays a role in the pathogenesis of this disease. Second, CD4+ memory T cells are enriched in the synovial tissue from patients with RA, and can be implicated through "guilt by association." Third, CD4+ T cells have been shown to be important in the initiation of arthritis in animal models. Fourth, T cell–directed therapies, such as cyclosporine and abatacept (CTLA4-Ig), have shown clinical efficacy in this disease. Taken together, these lines of evidence suggest that CD4+ T cells play an important role in orchestrating the chronic inflammatory response in RA. However, other cell types, such as CD8+ T cells, natural killer (NK) cells, and B cells are present in synovial tissue and may also influence pathogenic responses.

In the rheumatoid joint, by mechanisms of cell-cell contact and release of soluble mediators, activated T cells stimulate macrophages and fibroblast-like synoviocytes to generate proinflammatory mediators and proteases that drive the synovial inflammatory response and destroy the cartilage and bone. CD4+ T cells also provide help to B cells, which in turn, produce antibodies that may promote further inflammation in the joint. The previous T cell–centric model for the pathogenesis of RA was based on a T_H 1-driven paradigm, which came from studies indicating that CD4+ T helper (T_H) cells differentiated into T_H1 and T_H2 subsets, each with their distinctive cytokine profiles. T_H1 cells were found to mainly produce interferon γ (IFN-γ), lymphotoxin β, and TNF-α, while T_H2 cells predominately secreted interleukin (IL)-4, IL-5, IL-6, IL-10, and IL-13. The recent discovery of another subset of T_H cells, namely the T_H17 lineage, has revolutionized our concepts concerning the pathogenesis of RA. In humans, naïve T cells are induced to differentiate into T_H17 cells by exposure to transforming growth factor β (TGF-β), IL-1, IL-6, and IL-23. Upon activation, T_H17 cells secrete a variety of proinflammatory mediators such as IL-17, IL-21, IL-22, TNF-α, IL-26, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Substantial evidence now exists from both animal models and humans that IL-17 plays an important role not only in promoting joint inflammation but also in destroying cartilage and subchondral bone.

Activated B cells are also important players in the chronic inflammatory response. B cells give rise to plasma cells, which in turn, produce antibodies, including RF and anti-CCP antibodies. RFs may form large immune complexes inside the joint that contribute to the pathogenic process by fixing complement and promoting the release of proinflammatory chemokines and chemoattractants. In mouse models of arthritis, RF-containing immune complexes as well as anti-CCP-containing immune complexes synergize with other mechanisms to exacerbate the synovial inflammatory response.

RA is often considered to be a macrophage-driven disease because this cell type is the predominant source of proinflammatory cytokines inside the joint. Key proinflammatory cytokines released by synovial macrophages include TNF-α, IL-1, IL-6, IL-12, IL-15, IL-18, and IL-23. Synovial fibroblasts, the other major cell type in this microenvironment, produce the cytokines IL-1 and IL-6 as well as TNF-α. TNF-α is a pivotal cytokine in the pathobiology of synovial inflammation. It upregulates adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment. It also activates synovial fibroblasts, stimulates angiogenesis, promotes pain receptor sensitizing pathways, and drives osteoclastogenesis. Fibroblasts secrete matrix metalloproteinases (MMPs) as well as other proteases that are chiefly responsible for the breakdown of articular cartilage.

Osteoclast activation at the site of the pannus is closely tied to the presence of focal bone erosion. Receptor activator of nuclear factor κB ligand (RANKL) is expressed by stromal cells, synovial fibroblasts, and T cells. Upon binding to its receptor RANK on osteoclast progenitors, RANKL stimulates osteoclast differentiation and bone resorption. RANKL activity is regulated by osteoprotegerin (OPG), a decoy receptor of RANKL that blocks osteoclast formation. Monocytic cells in the synovium serve as the precursors of osteoclasts and, when exposed to macrophage colony-stimulating factor (M-CSF) and RANKL, fuse to form polykaryons termed *preosteoclasts*. These precursor cells undergo further differentiation into osteoclasts with the characteristic ruffled membrane. Cytokines such as TNF-α, IL-1, IL-6, and IL-17 increase the expression of RANKL in the joint and thus promote osteoclastogenesis. Osteoclasts also secrete cathepsin K, which is a cysteine protease that degrades the bone matrix by cleaving collagen.

Increased bone loss is only part of the story in RA, as decreased bone formation plays a crucial role in bone remodeling at sites of inflammation. Recent evidence shows that inflammation suppresses bone formation. The proinflammatory cytokine TNF-α plays a key role in actively suppressing bone formation by enhancing the expression of dickkopf-1 (DKK-1). DKK-1 is an important inhibitor of the Wnt pathway, which acts to promote osteoblast differentiation and bone formation. The Wnt system is a family of soluble glycoproteins that bind to cell-surface receptors known as frizzled (fz) and low-density lipoprotein (LDL) receptor–related proteins (LRPs) and promote cell growth. In animal models, increased levels of DKK-1 are associated with decreased bone formation, while inhibition of DKK-1 protects against structural damage in the joint. Wnt proteins also induce the formation of OPG and thereby shut down bone resorption, emphasizing their key role in tightly regulating the balance between bone resorption and formation.

DIAGNOSIS

The clinical diagnosis of RA is largely based on signs and symptoms of a chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information. In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy (Table 6-1). Application of the newly revised criteria yields a score of 0–10, with a score of ≥6 fulfilling the requirements for definite RA. The new classification criteria differ in several ways from the older criteria set. The new criteria include a positive test for serum anti-cyclic citrullinated peptide antibodies as an item, which carries greater specificity for the diagnosis of RA than a positive test for rheumatoid factor. The newer classification criteria also do not take into account if the patient has rheumatoid nodules or radiographic joint damage because these findings occur rarely in early RA. It is important to emphasize that the new 2010 ACR-EULAR criteria are "classification criteria" as opposed to "diagnostic criteria" and serve to distinguish patients at the onset of disease with a high likelihood of evolving into a chronic disease with persistent synovitis and joint damage. The presence of radiographic joint erosions or subcutaneous nodules may inform the diagnosis in the later stages of the disease.

TABLE 6-1

CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

		SCORE
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, Thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (≤3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	≥6 weeks	1

Note: These criteria are aimed at classification of newly presenting patients who have at least 1 joint with definite clinical synovitis that is not better explained by another disease.

Abbreviations: CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal.

Source: T Neogi et al: Arthritis Rheum 62:2569, 2010.

LABORATORY FEATURES

IgM, IgG, and IgA isotypes of RF occur in sera from patients with RA, although the IgM isotype is the one most frequently measured by commercial laboratories. Serum IgM RF has been found in 75–80% of patients with RA; therefore, a negative result does not exclude the presence of this disease. It is also found in other connective tissue diseases, such as primary Sjögren's syndrome, systemic lupus erythematosus, and type II mixed essential cryoglobulinemia, as well as chronic infections such as subacute bacterial endocarditis and hepatitis B and C. Serum RF may also be detected in 1–5% of the healthy population.

The presence of serum anti-CCP antibodies has about the same sensitivity as serum RF for the diagnosis of RA. However, its diagnostic specificity approaches 95%, so a positive test for anti-CCP antibodies in the setting of an early inflammatory arthritis is useful for distinguishing RA from other forms of arthritis. There is some incremental value in testing for the presence of both RF and anti-CCP, as some patients with RA are positive for RF, but negative for anti-CCP and visa versa. The presence of RF or anti-CCP antibodies also has prognostic significance, with anti-CCP antibodies showing the most value for predicting worse outcomes.

SYNOVIAL FLUID ANALYSIS

Typically, synovial fluid from patients with RA reflects an inflammatory state. Synovial fluid white blood cell (WBC) counts can vary widely, but generally range between 5000 and 50,000 WBC/μ^3 compared to <2000 WBC/μ for a non-inflammatory condition such as osteoarthritis. In contrast to the synovial tissue, the overwhelming cell type in the synovial fluid is the neutrophil. Synovial fluid also contains RF and anti-CCP antibodies and immune complexes, as well as by-products of complement activation. Clinically, the analysis of synovial fluid is most useful for confirming an inflammatory arthritis (as opposed to osteoarthritis), while at the same time excluding infection or a crystal-induced arthritis such as gout or pseudogout (Chap. 20).

JOINT IMAGING

Joint imaging is a valuable tool not only for diagnosing RA, but also for tracking progression of any joint

damage. Plain x-ray is the most common imaging modality, but it is limited to visualization of the bony structures and inferences about the state of the articular cartilage based on the amount of narrowing of the joint space. MRI and ultrasound techniques offer the added value of detecting changes in the soft tissues such as synovitis, tenosynovitis, and effusions as well as greater sensitivity for identifying bony abnormalities. Plain radiographs are usually relied upon in clinical practice for the purpose of diagnosis and monitoring of affected joints. However, in selected cases, MRI and ultrasound can provide additional diagnostic information that may guide clinical decision-making.

Plain radiography

Classically in RA, the initial radiographic finding is juxtaarticular osteopenia. Practically speaking, however, this finding is difficult to appreciate on plain films, and in particular, on the newer digitalized x-rays. Other findings on plain radiographs include soft tissue swelling, symmetric joint space loss, and subchondral erosions, most frequently in the wrists and hands (MCPs and PIPs) and the feet (MTPs). In the feet, the lateral aspect of the fifth MTP is often targeted first, but other MTP joints may be involved at the same time. X-ray imaging of advanced RA may reveal signs of severe destruction, including joint subluxation and collapse **(Fig. 6-5)**.

MRI

MRI offers the greatest sensitivity for detecting synovitis and joint effusions, as well as early bone and bone marrow changes. These soft tissue abnormalities often occur before osseous changes are noted on x-ray. Presence of bone marrow edema has been recognized to be an early sign of inflammatory joint disease, and can predict the subsequent development of erosions on plain radiographs as well as MRI scans. Cost and availability of MRI are the main factors limiting its routine clinical use.

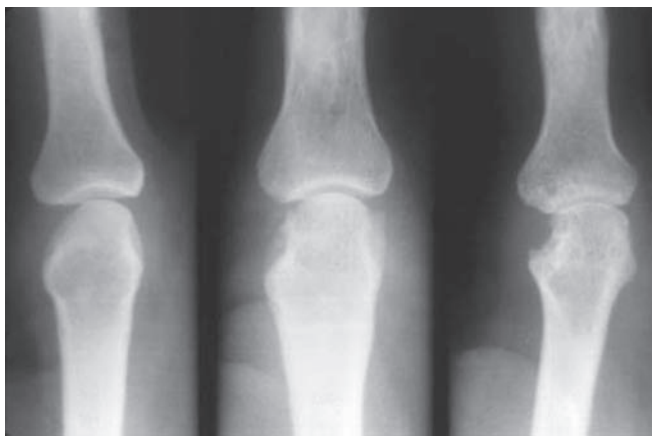


FIGURE 6-5
X-ray demonstrating progression of erosions on the proximal interphalangeal joint. (*Courtesy of the American College of Rheumatology.*)

Ultrasound

Ultrasound, including power color Doppler, has the ability to detect more erosions than plain radiography, especially in easily accessible joints. Less clear, however, is the ability of ultrasound to reliably detect synovitis, including increased joint vascularity indicative of inflammation. The usefulness of ultrasound is dependent on the experience of the sonographer; however, it does offer the advantages of portability, lack of radiation, and low expense relative to MRI, factors that make it attractive as a clinical tool.

CLINICAL COURSE

The natural history of RA is complex and affected by a number of factors including age of onset, gender, genotype, phenotype (i.e., extraarticular manifestations or variants of RA), and comorbid conditions, which make for a truly heterogeneous disease. There is no simple way to predict the clinical course. It is important to realize that as many as 10% of patients with inflammatory arthritis fulfilling ACR classification criteria for RA will undergo a spontaneous remission within 6 months (particularly seronegative patients). However, the vast majority of patients will exhibit a pattern of persistent and progressive disease activity that waxes and wanes in intensity over time. A minority of patients will show intermittent and recurrent explosive attacks of inflammatory arthritis interspersed with periods of disease quiescence. Finally, an aggressive form of RA may occur in an unfortunate few with inexorable progression of severe erosive joint disease, although this highly destructive course is less common in the modern treatment era of biologics.

Disability, as measured by the Health Assessment Questionnaire (HAQ), shows gradual worsening of disability over time in the face of poorly controlled disease activity and disease progression. Disability may result from both a disease activity–related component that is potentially reversible with therapy and a joint damage–related component owing to the cumulative and largely irreversible effects of cartilage and bone breakdown. Early in the course of disease, the extent of joint inflammation is the primary determinant of disability, while in the later stages of disease, the amount of joint damage is the dominant contributing factor. Previous studies have shown that more than one-half of patients with RA are unable to work 10 years after the onset of their disease; however, increased employability and less work absenteeism has been reported recently with the use of newer therapies and earlier treatment intervention.

The overall mortality rate in RA is two times greater than the general population, with ischemic heart disease being the most common cause of death followed by infection. Median life expectancy is shortened by an average of 7 years for men and 3 years for women compared to control populations. Patients at higher risk for shortened survival are those with systemic extraarticular involvement, low functional capacity, low socioeconomic status, low education, and chronic prednisone use.

TREATMENT Rheumatoid Arthritis

The amount of clinical disease activity in patients with RA reflects the overall burden of inflammation and is the variable most influencing treatment decisions. Joint inflammation is the main driver of joint damage and is the most important cause of functional disability in the early stages of disease. Several composite indices have been developed to assess clinical disease activity. The ACR 20, 50, and 70 improvement criteria [which corresponds to a 20%, 50%, and 70% improvement in joint counts, physician/patient assessment of disease severity, pain scale, serum levels of acute-phase reactants (ESR or CRP), and a functional assessment of disability using a self-administered patient questionnaire] are a composite index with a dichotomous response variable. The ACR improvement criteria are commonly used in clinical trials as an endpoint for comparing the proportion of responders between treatment groups. In contrast, the Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) are continuous measures of disease activity. These scales are increasingly used in clinical practice for tracking disease status, and in particular, for documenting treatment response.

Several developments during the past two decades have changed the therapeutic landscape in RA. They include: (1) the emergence of methotrexate as the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of early RA; (2) the development of novel highly efficacious biologicals that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone. The medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs (Table 6-2).

TABLE 6-2

DMARDS USED FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
Hydroxychloroquine	200–400 mg/d orally (≤6.5 mg/kg)	Irreversible retinal damage Cardiotoxicity Blood dyscrasia	Nausea Diarrhea Headache Rash	Eye examination if > 40 years old or prior ocular disease	Funduscopic and visual field testing every 12 months
Sulfasalazine	Initial: 500 mg orally twice daily Maintenance: 1000–1500 mg twice daily	Granulocytopenia Hemolytic anemia (with G6PD deficiency)	Nausea Diarrhea Headache	CBC, LFTs G6PD level	CBC every 2–4 weeks for first 3 months, then every 3 months
Methotrexate	10–25 mg/week orally or SQ Folic acid 1 mg/d to reduce toxicities	Hepatotoxicity Myelosuppression Infection Interstitial pneumonitis Pregnancy category X	Nausea Diarrhea Stomatitis/mouth ulcers Alopecia Fatigue	CBC, LFTs Viral hepatitis panel* Chest x-ray	CBC, creatinine, LFTs every 2–3 months
Leflunomide	10–20 mg/d	Hepatotoxicity Myelosuppression Infection Pregnancy category X	Alopecia Diarrhea	CBC, LFTs Viral hepatitis panel*	CBC, creatinine, LFTs every 2–3 months
TNF-α Inhibitors	Infliximab: 3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks. May increase dose up to 10 mg/kg every 4 weeks	↑ Risk bacterial, fungal infections Reactivation of latent TB ↑ Lymphoma risk (controversial) Drug-induced lupus Neurologic deficits	Infusion reaction ↑ LFTs	PPD skin test	LFTs periodically

(*continued*)

TABLE 6-2

DMARDS USED FOR THE TREATMENT OF RHEUMATOID ARTHRITIS (*CONTINUED*)

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
	Etanercept: 50 mg SQ weekly, or 25 mg SQ biweekly	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Adalimumab: 40 mg SQ every other week	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Golimumab: 50 mg SQ monthly	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Certolizumab: 400 mg SQ weeks 0, 2, 4 then 200 mg every other week	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
Abatacept SQ regimen: After a single IV loading dose (as per body weight categories above), 125 mg SQ should be given within a day, followed by 125 mg SQ once a week.	Weight based: <60 kg: 500 mg 60–100 kg: 750 mg >100 kg: 1000 mg IV dose at week 0, 2 and 4, and then every 4 weeks	↑ Risk bacterial, viral infections	Headache Nausea	PPD skin test	Monitor for infusion reactions
Anakinra	100 mg SQ daily	↑ Risk bacterial, viral infections Reactivation of latent TB Neutropenia	Injection site reaction Headache	PPD skin test CBC with differential	CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions
Rituximab	1000 mg IV × 2, day 0 and 14 May repeat course every 24 weeks or more Premedicate with methylprednisolone 100 mg to decrease infusion reaction	↑ Risk bacterial, viral infections Infusion reaction Cytopenia Hepatitis B reactivation	Rash Fever	CBC Viral hepatitis panel*	CBC at regular intervals
Tocilizumab	4–8 mg/kg 8 mg/kg IV monthly	Risk of infection Infusion reaction LFT elevation Dyslipidemia Cytopenias		PPD skin test	CBC and LFTs at regular intervals
Tofacitinib	5mg PO twice a day	Risk of infection Reactivation of TB Possible increased lymphoma risk Gastrointestinal perforation		CBC PPD skin test	CBC after 4-8 weeks then every 3 months LFTs at regular intervals Lipids after 4-8 weeks

*Viral hepatitis panel: hepatitis B surface antigen, hepatitis C viral antibody.

Abbreviations: CBC, complete blood count; DMARDs, disease-modifying anti-rheumatic drugs; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; LFTs, liver function tests; PPD, purified peptide derivative; SQ, subcutaneous; TB, tuberculosis.

While disease for some patients with RA is managed adequately with a single DMARD, such as methotrexate, the situation entails in most cases the use of a combination DMARD regimen that may vary in its components over the treatment course depending on fluctuations in disease activity and emergence of drug-related toxicities and comorbidities.

NSAIDS NSAIDs were formally viewed as the core of all other RA therapy, but they are now considered to be adjunctive therapy for management of symptoms uncontrolled by other measures. NSAIDs exhibit both analgesic and anti-inflammatory properties.

The anti-inflammatory effects of NSAIDs derive from their ability to nonselectively inhibit cyclooxygenase (COX)-1 and COX-2. Although the results of clinical trials suggest NSAIDs are roughly equivalent in their efficacy, experience suggests that some individuals may preferentially respond to a particular NSAID. Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

GLUCOCORTICOIDS Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low-to-moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1–2 week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5–10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy. Low-dose prednisone therapy has been shown in prospective studies to retard radiographic progression of joint disease; however, the benefits of this approach must be carefully weighed against the risks. Best practices minimize chronic use of low-dose prednisone therapy owing to the risk of osteoporosis and other long-term complications; however, the use of chronic prednisone therapy is unavoidable in many cases. Finally, if a patient exhibits one or a few actively inflamed joints, the clinician may consider intraarticular injection of an intermediate-acting glucocorticoid such as triamcinolone acetonide. This approach may allow for rapid control of inflammation in the setting of a limited number of affected joints. Caution must be exercised to appropriately exclude joint infection, as it often mimics an RA flare.

Osteoporosis ranks as an important long-term complication of chronic prednisone use. The ACR recommends primary prevention of glucocorticoid-induced osteoporosis with a bisphosphonate in any patient receiving 5 mg/d or more of prednisone for greater than 3 months. While prednisone use is known to increase the risk of peptic ulcer disease, especially with concomitant NSAID use, no evidence-based guidelines have been published regarding the use of gastrointestinal ulcer prophylaxis in this situation.

DMARDS DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of approximately 6–12 weeks. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. It was approved for the treatment of RA in 1986 and remains the benchmark for the efficacy and safety of new disease-modifying therapies. At the dosages used for the treatment of RA, methotrexate has been shown to stimulate adenosine release from cells, producing an anti-inflammatory effect. The clinical efficacy of leflunomide, an inhibitor of pyrimidine synthesis, appears similar to that of methotrexate; it has been shown in well-designed trials to be effective for the treatment of RA as monotherapy or in combination with methotrexate and other DMARDs.

Although similar to the other DMARDs in its slow onset of action, hydroxychloroquine has not been shown to delay radiographic progression of disease and thus is not considered to be a true DMARD. In clinical practice, hydroxychloroquine is generally used for treatment of early, mild disease or as adjunctive therapy in combination with other DMARDs. Sulfasalazine is utilized in a similar manner and has been shown in randomized, controlled trials to reduce radiographic progression of disease. Minocycline, gold salts, penicillamine, azathioprine, and cyclosporine have all been used for the treatment of RA with varying degrees of success; however, they are used sparingly now due to their inconsistent clinical efficacy or unfavorable toxicity profile.

BIOLOGICALS Biologic DMARDs have revolutionized the treatment of RA over the past decade (Table 6-2). They are protein therapeutics designed mostly to target cytokines and cell-surface molecules. The TNF inhibitors were the first biologicals approved for the treatment of RA. Anakinra, an IL-1 receptor antagonist, was approved shortly thereafter; however, its benefits have proved to be relatively modest compared with the other biologicals. Abatacept, rituximab, and tocilizumab are the newest members of this class.

Anti-TNF Agents The development of TNF inhibitors was originally spurred by the experimental finding that TNF is a critical upstream mediator of joint inflammation. Currently, five agents that inhibit TNF-α are approved for the treatment of RA. There are three different anti-TNF monoclonal antibodies. Infliximab is a

chimeric (part mouse and human) monoclonal antibody, while adalimumab and golimumab are humanized monoclonal antibodies. Certolizumab pegol is a pegylated Fc-free fragment of a humanized monoclonal antibody with binding specificity for TNF-α. Lastly, etanercept is a soluble fusion protein comprising the TNF receptor 2 in covalent linkage with the Fc portion of IgG1. All of the TNF inhibitors have been shown in randomized controlled clinical trials to reduce the signs and symptoms of RA, slow radiographic progression of joint damage, and improve physical function and quality of life. Anti-TNF drugs are typically used in combination with background methotrexate therapy. This combination regimen, which affords maximal benefit in many cases, is often the next step for treatment of patients with an inadequate response to methotrexate therapy. Etanercept, adalimumab, certolizumab pegol, and golimumab have also been approved for use as monotherapy.

Anti-TNF agents should be avoided in patients with active infection or a history of hypersensitivity to these agents. A major concern is the increased risk for infection, especially opportunistic fungal infection and reactivation of latent tuberculosis. For this reason, all patients are screened for latent tuberculosis according to national guidelines prior to starting anti-TNF therapy. In the United States, patients are skin tested using an intradermal injection of purified peptide derivative (PPD); individuals with skin reactions of more than 5 mm are presumed to have had previous exposure to TB and are evaluated for active disease and treated accordingly.

Anakinra Anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist, has seen limited use for the treatment of RA owing to its modest clinical efficacy. However, anakinra has enjoyed a resurgence of late for the treatment of some rare syndromes dependent on IL-1 production, including neonatal-onset inflammatory disease, Muckle-Wells syndrome, and familial cold urticaria, systemic juvenile-onset inflammatory arthritis, and adult-onset Still's disease. Anakinra should not be combined with an anti-TNF drug due to the high rate of serious infections as observed with this regimen in a clinical trial.

Abatacept Abatacept is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) linked to the modified portion of human IgG. It inhibits the co-stimulation of T cells by blocking CD28-CD80/86 interactions and may also inhibit the function of antigen-presenting cells by reverse signaling through CD80 and CD86. Abatacept has been shown in clinical trials to reduce disease activity, slow radiographic progression of damage, and improve functional disability. Most patients receive abatacept in combination with methotrexate or another DMARD such as leflunomide. Its onset of action is usually slower than that of the anti-TNF agents. Abatacept therapy has been associated with an increased risk of infection but is usually well tolerated otherwise.

Rituximab Rituximab is a chimeric monoclonal antibody directed against CD20, a cell-surface molecule expressed by most mature B-lymphocytes. It works by depleting B cells, which in turn, leads to a reduction in the inflammatory response by unknown mechanisms. Rituximab has been approved for the treatment of refractory RA in combination with methotrexate and has been shown to be more effective for patients with seropositive than seronegative disease. Rituximab therapy has been associated with mild-to-moderate infusion reactions as well as an increased risk of infection. Notably, there have been isolated reports of a potentially lethal brain disorder, progressive multifocal leukoencephalopathy (PML), in association with rituximab therapy, although the absolute risk of this complication appears to be very low in patients with RA. Most of these cases have occurred on a background of previous or current exposure to other potent immunosuppressive drugs.

Tocilizumab Tocilizumab is a humanized monoclonal antibody directed against the membrane and soluble forms of the IL-6 receptor. IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA, with detrimental effects on both joint inflammation and damage. IL-6 binding to its receptor activates intracellular signaling pathways that affect the acute-phase response, cytokine production, and osteoclast activation. Clinical trials have attested to the clinical efficacy of tocilizumab therapy for RA, both as monotherapy and in combination with methotrexate and other DMARDs. Tocilizumab has been associated with an increased risk of infection, neutropenia, and thrombocytopenia; however, the hematologic abnormalities appear to be reversible upon stopping the drug. In addition, this agent has been shown to increase LDL cholesterol; however, it is not known as yet if this effect on lipid levels increases the risk for development of atherosclerotic disease.

Tofacitinib Tofacitinib is a janus kinase (JAK) inhibitor which prevents the phosphorylation and activation of Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib, which is an orally administered agent, is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs. Tofacitinib has been associated with an increased risk of infection including tuberculosis and invasive fungal infections. Lymphoma and other malignancies have been observed. As gastroin-

testinal perforation has been reported, tofacitinib should be used with caution in patients at increased perforation risk. Laboratory abnormalities with tofacitinib have included lymphopenia, neutropenia, anemia, increased transaminases, and hyperlipidemia.

APPROACH TO THE PATIENT Rheumatoid Arthritis

The original treatment pyramid for RA is now considered to be obsolete and has evolved into a new strategy that focuses on several goals: (1) early, aggressive therapy to prevent joint damage and disability; (2) frequent modification of therapy with utilization of combination therapy where appropriate; (3) individualization of therapy in an attempt to maximize response and minimize side effects; and (4) achieving, whenever possible, remission of clinical disease activity. A considerable amount of evidence supports this intensive treatment approach.

As mentioned earlier, methotrexate is the DMARD of first choice for initial treatment of moderate-to-severe RA. Failure to achieve adequate improvement with methotrexate therapy calls for consideration of an effective combination regimen. Effective combinations include: methotrexate, sulfasalazine, and hydroxychloroquine (triple therapy); methotrexate and leflunomide; and methotrexate plus a biological. The combination of methotrexate and an anti-TNF agent, for example, has been shown in randomized, controlled trials to be superior to methotrexate alone not only for reducing signs and symptoms of disease, but also for retarding the progression of structural joint damage. The caveat of these studies, however, is that the protection against structural damage afforded by combining an anti-TNF drug with methotrexate appears to be restricted to a subset of patients with a high risk for disease progression. This subset corresponds to approximately 25% of patients enrolled in clinical trials. The remaining patients do not show significant progression in joint damage over 12 months while receiving methotrexate alone. Predicting which patients will ultimately show radiologic joint damage is imprecise at best, although some factors such as an elevated serum level of acute-phase reactants, high burden of joint inflammation, and the presence of erosive disease are associated with increased likelihood of developing structural injury.

Some patients may not respond to an anti-TNF drug or be intolerant of its side effects. Initial responders to an anti-TNF agent that later worsen may benefit from switching to another anti-TNF agent. Other biologicals, such as abatacept and rituximab, may also be considered for the treatment of patients whose disease is refractory to anti-TNF therapy. The addition of abatacept or rituximab to background methotrexate therapy has been shown in well-designed clinical trials to be effective for reducing the signs and symptoms of joint inflammation and slowing radiographic progression of disease. Early in the treatment course, abatacept may also be considered in lieu of an anti-TNF drug depending on the clinical circumstances (e.g., relative contraindication for the use of an anti-TNF agent).

A clinical state defined as low disease activity or remission is the optimal goal of therapy, although most patients never achieve remission despite every effort to achieve it. Composite indices, such as the Disease Activity Score-28 or DAS28, are useful for classifying states of low disease activity and remission; however, they are imperfect tools due to the limitations of the clinical joint examination in which low-grade synovitis may escape detection. Complete remission has been stringently defined as the total absence of all articular and extraarticular inflammation and immunologic activity related to RA. However, evidence for this state can be difficult to demonstrate in clinical practice. In an effort to standardize and simplify the definition of remission for clinical trials, the ACR and EULAR developed two provisional operational definitions of remission in RA (Table 6-3). A patient may be considered in remission if he or she 1) meets all of the clinical and laboratory criteria listed in Table 6-3 or 6-2) has a composite Simplified Disease Activity Index (SDAI) score of <3.3. The SDAI is calculated by taking the sum of a tender joint and swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and C-reactive protein (in mg/dL). This definition of remission does not take into account the possibility of subclinical synovitis or that damage alone may produce a tender or swollen joint. Ignoring the semantics of these definitions, the aforementioned remission criteria are nonetheless useful for setting a level of disease control that will likely result in minimal or no progression of structural damage and disability.

PHYSICAL THERAPY AND ASSISTIVE DEVICES All patients should receive a prescription for exercise and physical activity. Dynamic strength training, community-based comprehensive physical

TABLE 6-3

ACR/EULAR PROVISIONAL DEFINITION OF REMISSION IN RHEUMATOID ARTHRITIS

At any time point, patient must satisfy all of the following:
- Tender joint count ≤1
- Swollen joint count ≤1
- C-reactive protein ≤1 mg/dL
- Patient global assessment ≤1 (on a 0–10 scale)

OR

At any time point, patient must have a Simplified Disease Activity Index score of ≤3.3

Source: Adapted from DT Felson et al: Arthritis Rheum 63:573, 2011.

therapy, and physical-activity coaching (emphasizing 30 minutes of moderately intensive activity most days a week) have all been shown to improve muscle strength and perceived health status. Foot orthotics for painful valgus deformity decreases foot pain and resulting disability and functional limitations. Judicious use of wrist splints can also decrease pain; however, their benefits may be offset by decreased dexterity and a variable effect on grip strength.

SURGERY Surgical procedures may improve pain and disability in RA—most notably the hands, wrists, and feet, typically after the failure of medical therapy with varying degrees of reported long-term success. For large joints, such as the knee, hip, shoulder, or elbow, total joint arthroplasty is an option for advanced joint disease. A few surgical options exist for dealing with the smaller hand joints. Silicone implants are the most common prosthetic for MCP arthroplasty, and are generally implanted in patients with severe decreased arc of motion, marked flexion contractures, MCP joint pain with radiographic abnormalities and severe ulnar drift. Synovectomy and limited fusion are offered for the early rheumatoid wrist, but they are used much less frequently now compared to the past because of the availability of improved DMARD therapies. Arthrodesis and total wrist arthroplasty are reserved for patients with severe disease that have substantial pain and functional impairment. These two procedures appear to have equal efficacy in terms of pain control and patient satisfaction. Numerous surgical options exist for correction of hallux valgus in the forefoot, including arthrodesis and arthroplasty, as well as primarily arthrodesis for refractory hindfoot pain.

OTHER MANAGEMENT CONSIDERATIONS

Pregnancy Up to 75% of female RA patients will note overall improvement in symptoms during pregnancy, but often will flare post-delivery. Flares during pregnancy are generally treated with low doses of prednisone; hydroxychloroquine and sulfasalazine are probably the safest DMARDs to use during pregnancy. Methotrexate and leflunomide therapy are contraindicated during pregnancy due to their teratogenicity in animals and humans. The experience with biologic agents has been insufficient to make specific recommendations for their use during pregnancy. Most rheumatologists avoid their use in this setting; however, exceptions are considered depending on the circumstances.

Elderly Patients RA presents in up to one-third of patients after the age of 60; however, it has been recognized that older individuals receive less aggressive treatment due to concerns about increased risks of drug toxicity. Studies suggest that conventional DMARDs as well as biologic agents are equally effective and safe in younger and older patients. Due to comorbidities, many elderly patients have an increased risk of infection. Aging also leads to a gradual decline in renal function that may raise the risk for side effects from NSAIDs and some DMARDS, such as methotrexate. Renal function must be taken into consideration before prescribing methotrexate, which is mostly cleared by the kidneys. To reduce the risks of side effects, methotrexate doses may need to be adjusted downward for the drop in renal function that usually comes with the seventh and eighth decades of life. Methotrexate is usually not prescribed for patients with a serum creatinine greater than 2 mg/dl.

GLOBAL CHALLENGES



Developing countries are finding an increase in the incidence of noncommunicable, chronic diseases such as diabetes, cardiovascular disease, and RA in the face of ongoing poverty, rampant infectious disease, and poor access to modern health care facilities. In these areas, patients tend to have a greater delay in diagnosis and limited access to specialists, and thus greater disease activity and disability at presentation. In addition, infection risk remains a significant issue for the treatment of RA in developing countries because of the immunosuppression associated with the use of glucocorticoids and most DMARDs. For example, in some developing countries, patients undergoing treatment for RA have a substantial increase in the incidence of tuberculosis, which demands the implementation of far more comprehensive screening practices and liberal use of isoniazid prophylaxis than in developed countries. The increased prevalence of hepatitis B and C, as well as human immunodeficiency virus (HIV), in these developing countries also poses challenges. Reactivation of viral hepatitis has been observed in association with some of the DMARDs, such as rituximab. Also, reduced access to antiretroviral therapy may limit the control of HIV infection and therefore the choice of DMARD therapies.

Despite these challenges, one should attempt to implement early treatment of RA in the developing countries with the resources at hand. Sulfasalazine and methotrexate are all reasonably accessible throughout the world where they can be utilized as both monotherapy and in combination with other drugs. The use of biologic agents is increasing in the developed countries as well as in other areas around the world, although their use is limited by high cost; national protocols restrict their use, and concerns remain about the risk for opportunistic infections.

SUMMARY

Improved understanding of the pathogenesis of RA and its treatment has dramatically revolutionized the management of this disease. The outcomes of patients with RA are vastly superior to those of the prebiologic modifier era; more patients than in years past are able to avoid significant disability and continue working, albeit with some job modifications in many cases. The need for early and aggressive treatment of RA as well as frequent follow-up visits for monitoring of drug therapy has implications for our health care system. Primary care physicians and rheumatologists must be prepared to work together as a team to reach the ambitious goals of best practice. In many settings, rheumatologists have reengineered their practice in a way that places high priority on consultations for any new patient with early inflammatory arthritis.

The therapeutic regimens for RA are becoming increasingly complex with the rapidly expanding therapeutic armamentarium. Patients receiving these therapies must be carefully monitored by both the primary care physician and the rheumatologist to minimize the risk of side effects and identify quickly any complications of chronic immunosuppression. Also, prevention and treatment of RA-associated conditions such as ischemic heart disease and osteoporosis will likely benefit from a team approach owing to the value of multidisciplinary care.

Research will continue to search for new therapies with superior efficacy and safety profiles and investigate treatment strategies that can bring the disease under control more rapidly and nearer to remission. However, prevention and cure of RA will likely require new breakthroughs in our understanding of disease pathogenesis. These insights may come from genetic studies illuminating critical pathways in the mechanisms of joint inflammation. Equally ambitious is the lofty goal of biomarker discovery that will open the door to personalized medicine for the care of patients with RA.

CHAPTER 7

ACUTE RHEUMATIC FEVER

Jonathan R. Carapetis

Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A streptococcus. Although many parts of the body may be affected, almost all of the manifestations resolve completely. The exception is cardiac valvular damage [rheumatic heart disease (RHD)], which may persist after the other features have disappeared.

GLOBAL CONSIDERATIONS



ARF and RHD are diseases of poverty. They were common in all countries until the early twentieth century, when their incidence began to decline in industrialized nations. This decline was largely attributable to improved living conditions—particularly less crowded housing and better hygiene—which resulted in reduced transmission of group A streptococci. The introduction of antibiotics and improved systems of medical care had a supplemental effect. Recurrent outbreaks of ARF began in the 1980s in the Rocky Mountain states of the United States, where elevated rates persist.

The virtual disappearance of ARF and reduction in the incidence of RHD in industrialized countries during the twentieth century unfortunately was not replicated in developing countries, where these diseases continue unabated. RHD is the most common cause of heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well. It has been estimated that between 15 and 19 million people worldwide are affected by RHD, with approximately one-quarter of a million deaths occurring each year. Some 95% of ARF cases and RHD deaths now occur in developing countries.

Although ARF and RHD are relatively common in all developing countries, they occur at particularly elevated rates in certain regions. These "hot spots" are sub-Saharan Africa, Pacific nations, Australasia, and the Indian subcontinent **(Fig. 7-1)**. Unfortunately, most developing countries do not currently have coordinated, register-based RHD control programs, which are proven to be cost-effective in reducing the burden of RHD. Enhancing awareness of RHD and mobilizing resources for its control in developing countries is an issue requiring international attention.

EPIDEMIOLOGY

ARF is mainly a disease of children aged 5–14 years. Initial episodes become less common in older adolescents and young adults and are rare in persons aged >30 years. By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults. This pattern contrasts with the prevalence of RHD, which peaks between 25 and 40 years. There is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males.

PATHOGENESIS

ORGANISM FACTORS

Based on currently available evidence, ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci. Although classically, certain M-serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF, in high-incidence regions, it is now thought that any strain of group A streptococcus has the potential to cause ARF. Potential role of skin infection and of groups C and G streptococci are currently being investigated.

HOST FACTORS

Approximately 3–6% of any population may be susceptible to ARF, and this proportion does not vary

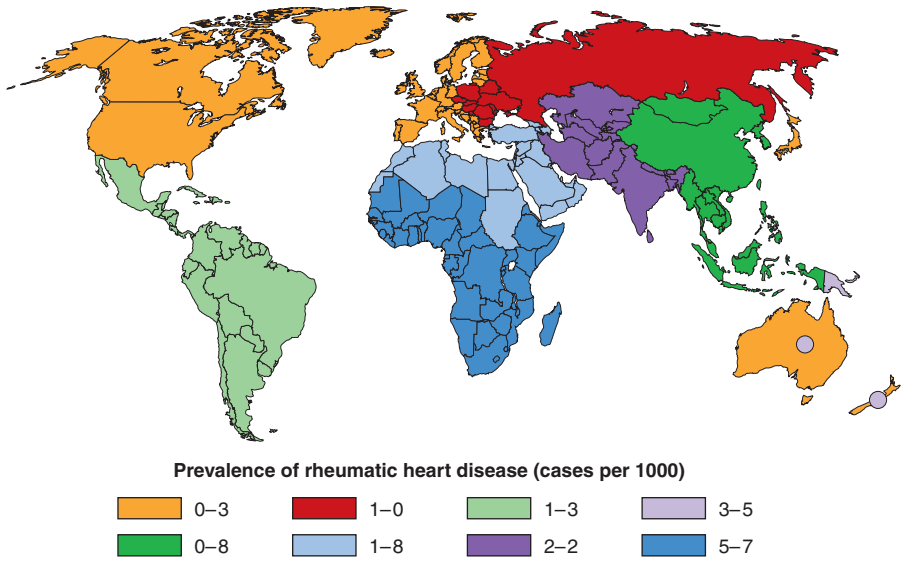


FIGURE 7-1

Prevalence of rheumatic heart disease in children aged 5–14 years. Circles within Australia and New Zealand represent indigenous populations, and also Pacific Islanders in New Zealand. (*From JR Carapetis et al: Lancet Infect Dis. Copyright 2005, with permission from Elsevier.*)

dramatically between populations. Findings of familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that susceptibility to ARF is an inherited characteristic. Particular human leukocyte antigen (HLA) class II alleles appear to be strongly associated with susceptibility. Associations have also been described with high levels of circulating mannose-binding lectin and polymorphisms of transforming growth factor β_1 gene and immunoglobulin genes. High-level expression of a particular alloantigen present on B cells, D8-17, has been found in patients with a history of ARF in many populations, with intermediate-level expression in first-degree family members, suggesting that this may be a marker of inherited susceptibility.

THE IMMUNE RESPONSE

When a susceptible host encounters a group A streptococcus, an autoimmune reaction results, which leads to damage to human tissues as a result of cross-reactivity between epitopes on the organism and the host **(Fig. 7-2)**. Cross-reactive epitopes are present in the streptococcal M protein and the *N*-acetylglucosamine of group A streptococcal carbohydrate and are immunologically similar to molecules in human myosin, tropomyosin, keratin, actin, laminin, vimentin, and *N*-acetylglucosamine. It is currently thought that the initial damage is due to cross-reactive antibodies attaching at the cardiac valve endothelium, allowing the entry of primed CD4+ T cells, leading to subsequent T cell-mediated inflammation.

CLINICAL FEATURES

There is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF. The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases it can only be confirmed using streptococcal antibody testing. The most common clinical presentation of ARF is polyarthritis and fever. Polyarthritis is present in 60–75% of cases and carditis in 50–60%. The prevalence of chorea in ARF varies substantially between populations, ranging from <2% to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

HEART INVOLVEMENT

Up to 60% of patients with ARF progress to RHD. The endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare. Early valvular damage leads to regurgitation. Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop **(Fig. 7-3)**. See Videos 7-1 and 7-2 that can be accessed via http://www.mhprofessional.com/HPIM18-Sectionals/.

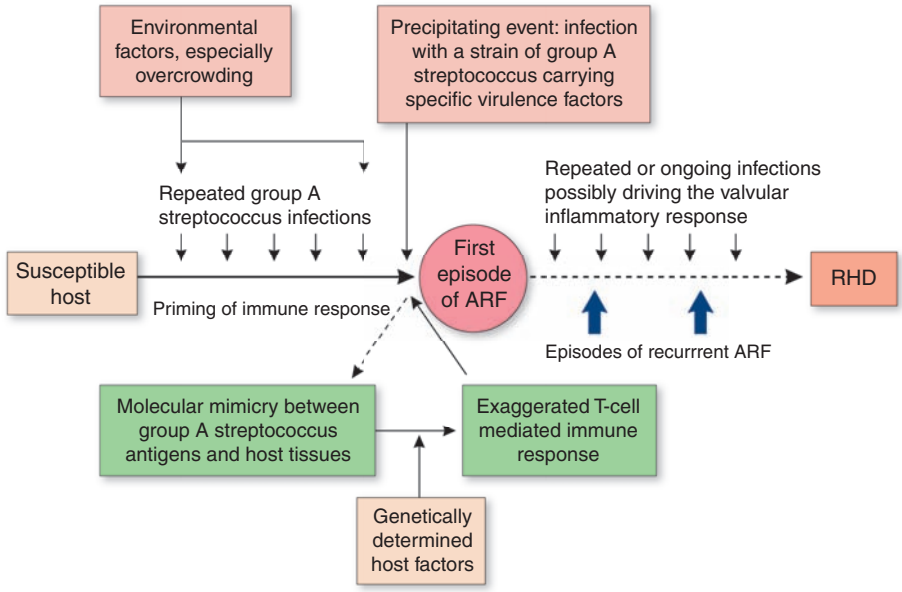


FIGURE 7-2
Pathogenetic pathway for acute rheumatic fever and rheumatic heart disease. (*From JR Carapetis et al: Lancet 366:155, 2005. Copyright 2005, with permission from Elsevier.*)

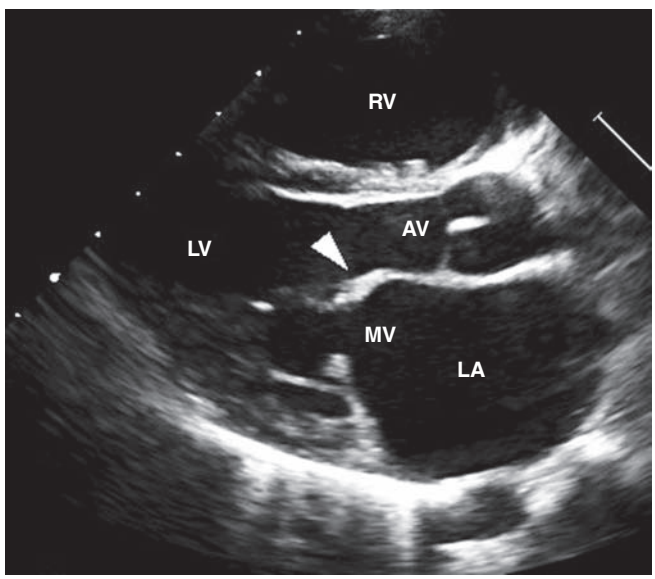


FIGURE 7-3
Transthoracic echocardiographic image from a 5-year-old boy with chronic rheumatic heart disease. This diastolic image demonstrates leaflet thickening, restriction of the anterior mitral valve leaflet tip, and doming of the body of the leaflet toward the interventricular septum. This appearance (marked by the arrowhead) is commonly described as a "hockey stick" or an "elbow" deformity. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (*Courtesy of Dr. Bo Remenyi, Department of Paediatric and Congential Cardiac Services, Starship Children's Hospital, Auckland, New Zealand.*)

Therefore the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation. Myocardial inflammation may affect electrical conduction pathways, leading to P-R interval prolongation (first-degree AV block or rarely higher-level block) and softening of the first heart sound.

JOINT INVOLVEMENT

To qualify as a major manifestation, joint involvement in ARF must be arthritic, i.e., objective evidence of inflammation, with hot, swollen, red and/or tender joints, and involvement of more than one joint (i.e., polyarthritis). The typical arthritis is migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints—most commonly the knees, ankles, hips, and elbows—and is asymmetric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

Less severe joint involvement is also relatively common but qualifies only as a minor manifestation. Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may be a presenting feature of ARF. This may occur because of early commencement of anti-inflammatory medication before the typical migratory pattern is established.

The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, joint involvement that persists more than 1 or 2 days after starting salicylates is unlikely

to be due to ARF. Conversely, if salicylates are commenced early in the illness, before fever and migratory polyarthritis have become manifest, it may be difficult to make a diagnosis of ARF. For this reason, salicylates and other NSAIDs should be withheld—and pain managed with acetaminophen or codeine—until the diagnosis is confirmed.

CHOREA

Sydenham's chorea commonly occurs in the absence of other manifestations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females. The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs. They may be generalized or restricted to one side of the body (hemi-chorea). The chorea varies in severity. In mild cases it may be evident only on careful examination, while in the most severe cases the affected individuals are unable to perform activities of daily living and are at risk of injuring themselves. Chorea eventually resolves completely, usually within 6 weeks.

SKIN MANIFESTATIONS

The classic rash of ARF is *erythema marginatum*, which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner's eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.

Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

OTHER FEATURES

Fever occurs in most cases of ARF, although rarely in cases of pure chorea. Although high-grade fever (≥39°C) is the rule, lower grade temperature elevations are not uncommon. Elevated acute-phase reactants are also present in most cases. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often dramatically elevated. Occasionally the peripheral leukocyte count is mildly elevated.

EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION

With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal infection is essential in making the diagnosis of ARF. As most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed. The most common serologic tests are the antistreptolysin O (ASO) and anti-DNase B (ADB) titers. Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection.

OTHER POST-STREPTOCOCCAL SYNDROMES THAT MAY BE CONFUSED WITH RHEUMATIC FEVER

Post-streptococcal reactive arthritis (PSRA) is differentiated from ARF on the basis of: (1) small-joint involvement that is often symmetric; (2) a short latent period following streptococcal infection (usually <1 week); (3) occasional causation by nongroup A β-hemolytic streptococcal infection; (4) slower responsiveness to salicylates; and (5) the absence of other features of ARF, particularly carditis.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) is a term that links a range of tic disorders and obsessive-compulsive symptoms with group A streptococcal infections. People with PANDAS are said not to be at risk of carditis, unlike patients with Sydenham's chorea. The diagnoses of PANDAS and PSRA should rarely be made in populations with a high incidence of ARF.

CONFIRMING THE DIAGNOSIS

Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection, and the exclusion of other diagnoses. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the *Jones criteria*) to aid in the diagnosis. An expert panel convened by the World Health Organization (WHO) clarified the use of the Jones criteria in ARF recurrences **(Table 7-1)**. Because each revision of the Jones criteria since 1944 has reduced sensitivity and increased specificity, in response to the decline in incidence of ARF in high-income countries, there is now concern that they may be too insensitive for countries where ARF incidence remains high. As a result, some countries (e.g., Australia and New Zealand) have developed their own, more sensitive, diagnostic criteria for ARF in their populations (links available at the *RHDnet* website www.worldheart.org/rhd).

TREATMENT Acute Rheumatic Fever

Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed, treatment

TABLE 7-1

2002–2003 WORLD HEALTH ORGANIZATION CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE (BASED ON THE 1992 REVISED JONES CRITERIA)

DIAGNOSTIC CATEGORIES	CRITERIA
Primary episode of rheumatic fever[a]	Two major or one major and two minor manifestations plus evidence of preceding group A streptococcal infection
Recurrent attack of rheumatic fever in a patient without established rheumatic heart disease	Two major or one major and two minor manifestations plus evidence of preceding group A streptococcal infection
Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease[b]	Two minor manifestations plus evidence of preceding group A streptococcal infection[c]
Rheumatic chorea Insidious onset rheumatic carditis[b]	Other major manifestations or evidence of group A streptococcal infection not required
Chronic valve lesions of rheumatic heart disease (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease)[d]	Do not require any other criteria to be diagnosed as having rheumatic heart disease
Major manifestations	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules
Minor manifestations	Clinical: fever, polyarthralgia Laboratory: elevated erythrocyte sedimentation rate or leukocyte count[e] Electrocardiogram: prolonged P-R interval
Supporting evidence of a preceding streptococcal infection within the last 45 days	Elevated or rising anti-streptolysin O or other streptococcal antibody, *or* A positive throat culture, *or* Rapid antigen test for group A streptococcus, *or* Recent scarlet fever[e]

[a]Patients may present with polyarthritis (or with only polyarthralgia or monoarthritis) and with several (three or more) other minor manifestations, together with evidence of recent group A streptococcal infection. Some of these cases may later turn out to be rheumatic fever. It is prudent to consider them as cases of "probable rheumatic fever" (once other diagnoses are excluded) and advise regular secondary prophylaxis. Such patients require close follow-up and regular examination of the heart. This cautious approach is particularly suitable for patients in vulnerable age groups in high incidence settings.

[b]Infective endocarditis should be excluded.

[c]Some patients with recurrent attacks may not fulfill these criteria.

[d]Congenital heart disease should be excluded.

[e]1992 Revised Jones criteria do not include elevated leukocyte count as a laboratory minor manifestation (but do include elevated C-reactive protein), and do not include recent scarlet fever as supporting evidence of a recent streptococcal infection.

Source: Reprinted with permission from WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease (2001: Geneva, Switzerland): *Rheumatic Fever and Rheumatic Heart Disease: Report of a WHO Expert Consultation* (WHO Tech Rep Ser, 923). Geneva, World Health Organization, 2004.

of heart failure and other symptoms is undertaken, and preventive measures including commencement of secondary prophylaxis, inclusion on an ARF registry, and health education are commenced. Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determine the severity at baseline of any carditis. Other tests that should be performed are listed in Table 7-2.

There is no treatment for ARF that has been proven to alter the likelihood of developing, or the severity of, RHD. With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptomatic.

ANTIBIOTICS All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection. Penicillin is the drug of choice and can be given orally [as phenoxymethyl penicillin, 500 mg (250 mg for children ≤27 kg) PO twice daily, or amoxicillin 50 mg/kg (max 1 g) daily, for 10 days] or as a single dose of 1.2 million units (600,000 units for children ≤27 kg) IM benzathine penicillin G.

SALICYLATES AND NSAIDS These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed. They are of no proven value in the treatment of carditis or chorea. Aspirin is

TABLE 7-2

RECOMMENDED TESTS IN CASES OF POSSIBLE ACUTE RHEUMATIC FEVER

Recommended for all cases
- White blood cell count
- Erythrocyte sedimentation rate
- C-reactive protein
- Blood cultures if febrile
- Electrocardiogram (repeat in 2 weeks and 2 months if prolonged P-R interval or other rhythm abnormality)
- Chest x-ray if clinical or echocardiographic evidence of carditis
- Echocardiogram (consider repeating after 1 month if negative)
- Throat swab (preferably before giving antibiotics)–culture for group A streptococcus
- Anti-streptococcal serology: both anti-streptolysin O and anti-DNase B titres, if available (repeat 10–14 days later if 1st test not confirmatory)

Tests for alternative diagnoses, depending on clinical features
- Repeated blood cultures if possible endocarditis
- Joint aspirate (microscopy and culture) for possible septic arthritis
- Copper, ceruloplasmin, anti-nuclear antibody, drug screen for choreiform movements
- Serology and auto-immune markers for arboviral, auto-immune or reactive arthritis

Source: Reprinted with permission from National Heart Foundation of Australia: *Diagnosis and Management of Acute Rheumatic Fever and Heart Disease in Australia: Complete Evidence-Based Review and Guideline*. Melbourne, National Heart Foundation of Australia, 2006.

the drug of choice. An initial dose of 80–100 mg/kg per day in children (4–8 g/d in adults) in 4–5 divided doses is often needed for the first few days up to 2 weeks. A lower dose should be used if symptoms of salicylate toxicity emerge, such as nausea, vomiting, or tinnitus. When the acute symptoms are substantially resolved, the dose can be reduced to 60–70 mg/kg per day for a further 2–4 weeks. Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued. This does not indicate a recurrence and can be managed by recommencing salicylates for a brief period. Although less well studied, naproxen at a dose of 10–20 mg/kg per day has been reported to lead to good symptomatic response.

CONGESTIVE HEART FAILURE

Glucocorticoids The use of glucocorticoids in ARF remains controversial. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or salicylates in improving the short- or longer term outcome of carditis. However, the studies included in these meta-analyses all took place >40 years ago and did not use medications in common usage today. Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However, the potential benefits of this treatment should be balanced against the possible adverse effects, including gastrointestinal bleeding and fluid retention. If used, prednisone or prednisolone are recommended at doses of 1–2 mg/kg per day (maximum, 80 mg). Glucocorticoids are often only required for a few days or up to a maximum of 3 weeks.

Other Therapies Patients may require therapeutic approaches as would be used to manage congestive heart failure occurring due to other etiologies.

BED REST Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present, and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.

CHOREA Medications to control the abnormal movements do not alter the duration or outcome of chorea. Milder cases can usually be managed by providing a calm environment. In patients with severe chorea, carbamazepine or sodium valproate are preferred to haloperidol. A response may not be seen for 1–2 weeks, and a successful response may only be to reduce rather than resolve the abnormal movements. Medication should be continued for 1–2 weeks after symptoms subside.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) Small studies have suggested that IVIg may lead to more rapid resolution of chorea but has shown no benefit on the short- or long-term outcome of carditis in ARF without chorea. In the absence of better data, IVIg is *not* recommended except in cases of severe chorea refractory to other treatments.

PROGNOSIS

Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks. Inflammatory markers should be monitored every 1–2 weeks until they have normalized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis. Cases with more severe carditis need close clinical and echocardiographic monitoring in the longer term.

Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners

to ensure a plan for follow-up and administration of secondary prophylaxis before the patient is discharged. Patients and their families should also be educated about their disease, emphasizing the importance of adherence to secondary prophylaxis. If carditis is present, they should also be informed of the need for antibiotic prophylaxis against endocarditis for dental and surgical procedures.

PREVENTION

PRIMARY PREVENTION

Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing. This is difficult to achieve in most places where ARF is common.

Therefore, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin (as outlined earlier for treatment of ARF) will prevent almost all cases of ARF that would otherwise have developed. This important strategy relies on individuals presenting for medical care when they have a sore throat, the availability of trained health and microbiology staff along with the materials and infrastructure to take throat swabs, and a reliable supply of penicillin. Unfortunately, many of these elements are not available in developing countries.

SECONDARY PREVENTION

The mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤27 kg) delivered every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with 4-weekly dosing can be achieved, more frequent dosing is rarely needed. Oral penicillin V (250 mg) can be given twice-daily instead, but is somewhat less effective than benzathine penicillin G. Penicillin allergic patients can receive erythromycin (250 mg) twice daily.

The duration of secondary prophylaxis is determined by many factors, in particular the duration since the last episode of ARF (recurrences become less likely with increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence because of the potentially serious consequences) **(Table 7-3)**. Secondary prophylaxis is best delivered as part of a coordinated RHD control program, based around a registry of patients. Registries improve the ability to follow patients and identify those who default from prophylaxis and institute strategies to improve adherence.

TABLE 7-3

AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR DURATION OF SECONDARY PROPHYLAXIS*

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer). Sometimes lifelong prophylaxis.

*These are only recommendations and must be modified by individual circumstances as warranted. Note that other organizations have slightly different recommendations (see www.worldheart.org/rhd for links).

Source: Adapted from AHA Scientific Statement Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis. Circulation 119:1541, 2009.

CHAPTER 8

SYSTEMIC SCLEROSIS (SCLERODERMA) AND RELATED DISORDERS

John Varga

DEFINITION

Systemic sclerosis (SSc) is a connective tissue disorder of unknown etiology, heterogeneous clinical manifestations, and chronic and often progressive course. The diffuse cutaneous form of SSc (dcSSc) is characterized by thickening of the skin (scleroderma) and distinctive involvement of multiple internal organs, most notably the lungs, gastrointestinal tract, heart, and kidneys. The early stage of the disease is associated with prominent inflammatory features. Over time, patients develop functional and structural alterations in multiple vascular beds and progressive visceral organ dysfunction due to fibrosis. Although the presence of thickened skin (scleroderma) distinguishes SSc from other connective tissue diseases, scleroderma-like skin induration can occur in localized forms of scleroderma and other disorders **(Table 8-1)**. Patients can be classified into two principal subsets defined largely by the pattern of skin involvement, as well as clinical and laboratory manifestations **(Table 8-2)**. Diffuse cutaneous SSc is associated with progressive skin induration, starting in the fingers and ascending from distal to proximal extremities, the face, and the trunk. These patients are at risk for early pulmonary fibrosis and acute renal involvement. Patients with limited cutaneous SSc (lcSSc) generally have long-standing Raynaud's phenomenon before other manifestations of SSc appear. Skin involvement in lcSSc is slowly progressive and remains limited to the fingers (sclerodactyly), distal extremities, and face, but the trunk is not affected. A subset of patients with lcSSc have prominent calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, a constellation termed *CREST syndrome.* However, these features may also be seen in patients with dcSSc. Visceral organ involvement in lcSSc tends to show insidious progression. Although the long-term prognosis of lcSSc is better than that of dcSSc, pulmonary arterial hypertension (PAH), interstitial lung disease, hypothyroidism, and primary biliary cirrhosis may develop in the late stage of lcSSc. In some patients, Raynaud's phenomenon and other typical features of SSc occur in the absence of detectable skin thickening. This syndrome has been termed *SSc sine scleroderma.*

TABLE 8-1

CONDITIONS ASSOCIATED WITH SCLERODERMA-LIKE INDURATION

Systemic sclerosis (SSc)
Limited cutaneous SSc
Diffuse cutaneous SSc
Localized scleroderma
Guttate morphea, diffuse morphea
Linear scleroderma, coup de sabre, hemifacial atrophy
Pansclerotic morphea
Overlap syndromes
Mixed connective tissue disease
SSc/polymyositis
Stiff Skin Syndrome
Undifferentiated connective tissue disease
Scleredema and diabetic scleredema
Scleromyxedema (papular mucinosis)
Nephrogenic systemic fibrosis (nephrogenic fibrosing dermatopathy)
Chronic graft-versus-host disease
Diffuse fasciitis with eosinophilia (Shulman disease, eosinophilic fasciitis)
Eosinophilia-myalgia syndrome
Chemically induced scleroderma-like conditions
Vinyl chloride–induced disease
Pentazocine-induced skin fibrosis
Paraneoplastic syndrome

TABLE 8-2

SUBSETS OF SYSTEMIC SCLEROSIS (SSc): LIMITED CUTANEOUS SSc VERSUS DIFFUSE CUTANEOUS SSc

FEATURES	LIMITED CUTANEOUS SSc	DIFFUSE CUTANEOUS SSc
Skin involvement	Indolent onset. Limited to fingers, distal to elbows, face; slow progression	Rapid onset. Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Precedes skin involvement; associated with critical ischemia	Onset coincident with skin involvement, may be mild
Musculoskeletal	Early arthralgia, fatigue	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs
Pulmonary fibrosis	Occasional, moderate	Frequent, early and severe
Pulmonary arterial hypertension	Frequent, late, may be isolated	May occur, often in association with pulmonary fibrosis
Scleroderma renal crisis	Very rare	Occurs in 15%; early
Calcinosis cutis	Frequent, prominent	May occur, mild
Characteristic autoantibodies	Anticentromere	Antitopoisomerase I (Scl-70), anti-RNA polymerase III

EPIDEMIOLOGY

SSc is an acquired sporadic disease with a worldwide distribution and affecting all races. In the United States, the incidence is estimated at 9–19 cases per million per year. The only community-based survey of SSc yielded a prevalence of 286 cases per million population. There are an estimated 100,000 cases in the United States, although this number may be significantly higher if patients who do not meet strict classification criteria are also included. Studies from England, Australia, and Japan showed rates of SSc that were lower than in the United States. Age, gender, and ethnicity are important factors determining disease susceptibility. Like other connective tissue diseases, SSc shows a female predominance that is most pronounced in the childbearing years and declines after menopause. While SSc can present at any age, the most common age of onset for both limited and diffuse cutaneous forms is in the range of 30–50 years. The incidence is higher in blacks than whites, and disease onset occurs at an earlier age. Furthermore, blacks are more likely to have the diffuse cutaneous form of SSc associated with interstitial lung involvement and a worse prognosis.

GENETIC CONSIDERATIONS



SSc shows a non-Mendelian pattern of inheritance. Monozygotic twins have a relatively low concordance rate for SSc (4.7%), although concordance for antinuclear antibodies is significantly greater. A genetic contribution to disease susceptibility is indicated by the fact that 1.6% of SSc patients have a first-degree relative with SSc, a prevalence rate substantially higher than in the general population. The risk of other autoimmune diseases, including systemic lupus erythematosus (SLE) (Chap. 4) and rheumatoid arthritis (Chap. 6), is also increased. Among Choctaw Indians from Oklahoma, SSc prevalence as high as 4690 per million has been reported. Genetic investigations in SSc have focused on candidate gene polymorphisms. Small studies have shown associations with the genes encoding angiotensin-converting enzyme (ACE); endothelin-1 and nitric oxide synthase; B cell markers (CD19); chemokines (monocyte chemoattractant protein-1) and chemokine receptors; interferon signaling mediators STAT4 and IRF5; migration inhibitory factor; cytokines [interleukin 1α (IL-1α, IL-4, and tumor necrosis factor α (TNF-α)]; growth factors and their receptors [connective tissue growth factor (CTGF) and transforming growth factor β (TGF-β)]; and extracellular matrix proteins [fibronectin, fibrillin, and secreted protein acidic-rich in cysteine (SPARC)]. To date, these genetic studies indicate that as in other complex diseases, multiple genetic loci are involved in SSc, and their individual contributions to disease susceptibility are modest. Genome-wise association studies to identify additional genetic susceptibility loci in SSc are currently underway.

ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS

Patients with SSc have increased serum antibodies to human cytomegalovirus (hCMV), and antitopoisomerase-I (Scl-70) autoantibodies recognize antigenic epitopes present on the hCMV-derived proteins, suggesting molecular mimicry as a possible mechanistic link between hCMV

infection and SSc. Evidence of human parvovirus B19 infection in SSc patients has also been presented; however, the etiologic role of viruses remains unproven. Reports of geographic clustering of SSc cases suggesting shared environmental exposures have not been substantiated by careful investigation. An epidemic of a novel syndrome with features suggestive of SSc occurred in Spain in the 1980s. The outbreak, termed *toxic oil syndrome* and affecting over 20,000 individuals, was linked to contaminated rapeseed oils used for cooking. A similar epidemic outbreak, termed *eosinophilia-myalgia syndrome* (EMS), occurred a decade later in the United States. Affected individuals presented with marked eosinophilia and severe myalgia, followed by the development of scleroderma-like chronic skin lesions. The EMS epidemic was linked to the consumption of imported batches of L-tryptophan used as dietary supplements. While both of these apparently novel toxic-epidemic syndromes were characterized by scleroderma-like chronic skin changes and variable visceral organ involvement they were associated with clinical, pathologic, and laboratory features that clearly distinguished them from SSc. The incidence of SSc is increased among miners exposed to silica. Other occupational exposures tentatively linked with SSc include polyvinyl chloride, epoxy resins, and aromatic hydrocarbons including toluene and trichloroethylene. Drugs implicated in SSc-like illnesses include bleomycin, pentazocine and cocaine, and appetite suppressants linked with pulmonary hypertension. As yet unknown inhaled factors may play a role in the development of SSc-associated interstitial lung disease. Case reports and series describing SSc in women with silicone breast implants had raised concern regarding a possible causal role of silicone in SSc. However, large-scale epidemiologic investigations found no evidence of increased risk of SSc.

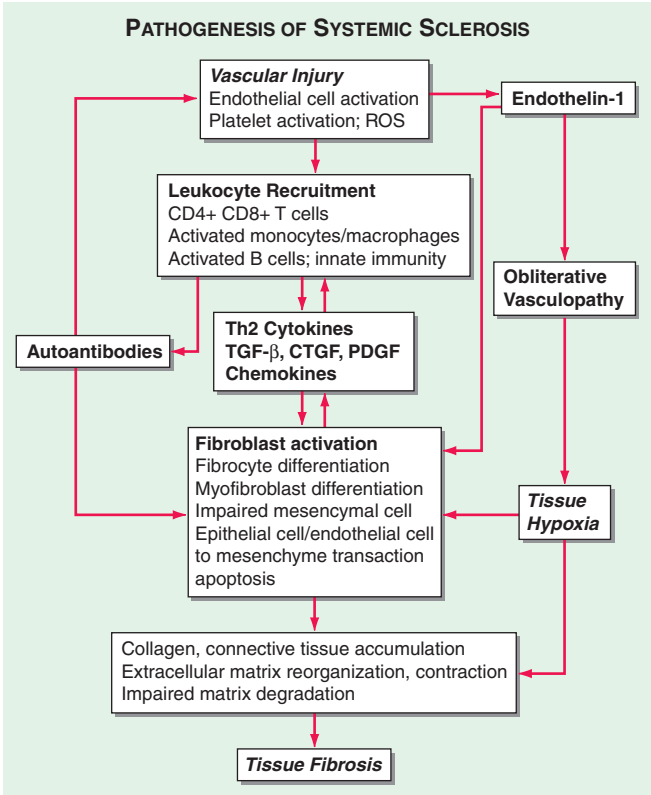


FIGURE 8-1

Initial vascular injury in a genetically susceptible individual leads to functional and structural vascular alterations, inflammation, and autoimmunity. The inflammatory and immune responses initiate and sustain fibroblast activation and differentiation, resulting in pathologic fibrogenesis and irreversible tissue damage. Vascular damage results in tissue ischemia that further contributes to progressive fibrosis and atrophy. CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β.

PATHOGENESIS

A comprehensive view of the pathogenesis of SSc must incorporate the three cardinal features of the disease: (1) vasculopathy, (2) cellular and humoral auto immunity, and (3) progressive visceral and vascular fibrosis in multiple organs **(Fig. 8-1)**. Autoimmunity and altered vascular reactivity may be the earliest manifestations of SSc. Complex interplay between these processes is thought to initiate and then amplify the fibrotic process.

ANIMAL MODELS OF DISEASE

There is no single animal model of SSc that reproduces the three cardinal processes that underlie the pathogenesis, but some models recapitulate selected disease characteristics. The tight-skin mouse (Tsk1) is a naturally occurring fibrosis model characterized by spontaneous skin thickening. The mutation responsible for the phenotype, a duplication in the fibrillin-1 gene, gives rise to an abnormally large fibrillin-1 protein that contributes to defective extracellular matrix assembly and aberrant activation of TGF-β. Mutations in the fibrillin-1 gene are associated with Marfan's disease and the stiff skin syndrome but have not been described in patients with SSc. Fibrosis in the skin and lungs can be induced in mice by bleomycin injections or by transplantation of human leukocyte antigen (HLA)-mismatched bone marrow or spleen cells. Increasingly, manipulation of mice via mutagenesis or targeted genetic modification such as knock-out or transgenesis are utilized to create new disease models and for dissecting the roles of individual molecules in the underlying processes. For example, genetic targeting of Smad3, an intracellular TGF-β signal transducer, or of the nuclear receptor peroxisome proliferator-activated receptor (PPAR) gamma, yielded mice that were resistant or hypersensitive to bleomycin-induced scleroderma. These mouse models become increasingly useful for preclinical testing of novel treatments.

MICROANGIOPATHY

Vascular involvement in SSc is extensive, involves multiple vascular beds, and has important clinical consequences. Raynaud's phenomenon, an early manifestation, is characterized by an altered blood-flow response to cold challenge. This initially reversible functional vascular abnormality is associated with alterations in the autonomic and peripheral nervous systems, with impaired production of neuropeptides such as calcitonin gene-related peptide from sensory afferent nerves and heightened sensitivity of α_2-adrenergic receptors on vascular smooth-muscle cells. While isolated Raynaud's phenomenon is common, relatively benign, and nonprogressive, SSc-associated Raynaud's phenomenon is frequently complicated by irreversible structural and functional changes. Viruses, superoxide radicals, vascular cytotoxic factors, and immune responses such as complement and circulating autoantibodies to endothelial cells may each contribute to endothelial cell injury in early SSc. Endothelial injury results in dysregulated production of endothelium-derived vasodilatory (nitric oxide and prostacyclin) and vasoconstricting (endothelin-1) substances, as well as increased expression of intercellular adhesion molecule 1 (ICAM-1) and other surface adhesion molecules. Microvessels show enhanced permeability and transendothelial leukocyte diapedesis, activation of coagulation and fibrinolytic cascades, and platelet aggregation. Smooth muscle cell–like myointimal cells proliferate, the basement membrane is thickened and reduplicated, and fibrosis of the adventitial layers develops. The vasculopathic process affects capillaries, as well as arterioles, and even large vessels in many organs, resulting in reduced blood flow, tissue ischemia, and generation of profibrotic factors. Progressive luminal occlusion due to intimal and medial hypertrophy, combined with persistent endothelial cell damage and adventitial fibrosis, establish a vicious cycle culminating in the striking absence of blood vessels seen on angiograms of the hands and kidneys in late-stage disease. Damaged endothelium promotes platelet aggregation with release of serotonin and platelet alpha granules including thromboxane, a potent vasoconstrictor, and of platelet-derived growth factor (PDGF). Vascular compromise is aggravated by defective fibrinolysis. Oxidative stress due to ischemia-reperfusion is associated with generation of reactive oxygen species (ROS) that further damage the endothelium through peroxidation of membrane lipids. Paradoxically, the process of revascularization that normally reestablishes blood flow to ischemic tissue is defective in SSc despite elevated levels of vascular endothelial growth factor (VEGF) and other angiogenic factors. The number of bone marrow–derived CD34+ CD133+ endothelial progenitor cells is markedly reduced in the circulation, and their differentiation in vitro into mature endothelial cells is impaired. Thus, widespread capillary malformation and loss, obliterative vasculopathy of small and medium-sized arteries, and failure to repair damaged vessels are hallmarks of SSc.

INFLAMMATION AND CELLULAR IMMUNITY

In the early stages of SSc, activated T cells and monocytes/macrophages accumulate in lesional skin, lungs, and other affected organs. Infiltrating T cells express CD45 and HLA-DR activation markers and display restricted T cell receptor signatures indicative of oligoclonal expansion in response to (unknown) antigen. Circulating CD4+ T cells have elevated levels of chemokine receptors and α_1 integrin adhesion molecules, accounting for their enhanced ability to bind to endothelium and to fibroblasts. Endothelial cells express ICAM-1 and other adhesion molecules that facilitate leukocyte diapedesis. Activated macrophages and T cells show a T_H2-polarized immune response and secrete IL-4 and IL-13. T_H2 cytokines induce the production of TGF-β and promote collagen synthesis and other profibrotic responses, whereas the T_H1 cytokine interferon γ (IFN-γ) inhibits collagen synthesis and blocks cytokine-mediated fibroblast activation. Because TGF-β stimulates its own synthesis, as well as that of CTGF (also termed CCN2) and other cytokines, TGF-β establishes an autocrine/paracrine stimulatory loop that sustains activation of fibroblasts and other effector cells (Chaps. 1 and 3). Regulatory T cells (Tregs) are essential for maintaining normal immune tolerance. While the frequency of Tregs in the peripheral blood is elevated in SSc, their immunosuppressive function is defective.

Humoral autoimmunity

Antinuclear antibodies occur in virtually all patients with SSc. In addition, a number of mutually exclusive autoantibodies that are highly specific for SSc have been described. These antibodies show strong association with specific disease phenotypes and genetically determined HLA haplotypes **(Table 8-3)**. Autoantibody levels correlate with disease severity, and titers fluctuate with disease activity. While some SSc-specific autoantibodies are antinuclear and directed against intracellular proteins such as topoisomerase-I, and the RNA polymerases, others are directed against cell-surface antigens or secreted proteins. Functional autoantibodies have well-established clinical utility as diagnostic and prognostic markers in SSc, although their pathogenetic role in the disease manifestations remains uncertain. Autoantibodies to fibroblasts, endothelial cells, PDGF cell-surface receptors, fibrillin-1, and matrix metalloproteinase enzymes have been described in SSc. The direct pathogenetic role of these self antibodies in SSc remains to be firmly established.

TABLE 8-3

AUTOANTIBODIES AND ASSOCIATED FEATURES IN SYSTEMIC SCLEROSIS (SSc)

TARGET ANTIGEN	SSc SUBSET	CHARACTERISTIC CLINICAL ASSOCIATION
Topoisomerase-I	dcSSc	Tendon friction rubs, ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins	lcSSc	Digital ischemia, calcinosis, isolated PAH; renal crisis rare
RNA polymerase III	dcSSc	Extensive skin, tendon friction rubs, renal crisis
U3-RNP	dcSSc	PAH, ILD, scleroderma renal crisis, myositis
Th/T0	lcSSc	ILD, PAH
PM/Scl	lcSSc	Calcinosis, myositis
U1-RNP	MCTD	PAH

Abbreviations: dcSSc, diffuse cutaneous SSc; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension.

A variety of mechanisms have been proposed for the occurrence of autoantibodies in SSc. Proteolytic cleavage, increased expression, or altered subcellular localization of certain cellular proteins in SSc could lead to their recognition as neoepitopes by the immune system. For example, cytotoxic T cells release the protease granzyme B that cleaves peptides, and generates neoepitopes that can break immune tolerance. Recent studies implicate B cells in both the autoimmune and fibrotic responses in SSc. In addition to their well-recognized role in antibody production, B cells can also present antigen, produce IL-6 and TGF-β, and modulate T cell and dendritic cell function. In SSc, B cells show elevated CD19 expression, and reduced numbers of memory B cells and early plasma cells. Gene expression profiling of lesional skin has identified mRNA expression signatures characteristic of B cell activation.

FIBROSIS

Fibrosis affecting multiple organs distinguishes SSc from other connective tissue diseases. Fibrosis characteristically follows, and is thought to be a consequence of, autoimmunity and vascular damage. The process, characterized by progressive replacement of normal tissue architecture with dense connective tissue, accounts for substantial morbidity and mortality. Fibroblasts are mesenchymal cells responsible for maintaining the functional and structural integrity of connective tissue. When activated by TGF-β and related factors, fibroblasts proliferate, migrate, secrete collagens and extracellular matrix, growth factors, and cytokines, and transdifferentiate into myofibroblasts. Under normal conditions, these responses allow fibroblasts to repair tissue damage. The rapid and self-limited physiologic repair program becomes sustained and amplified in pathologic fibrosis, resulting in the irreversible accumulation of scar tissue.

In addition to connective tissue–resident fibroblasts, and transformation of epithelial cells into fibroblasts, circulating mesenchymal progenitor cells of bone marrow origin might also contribute to fibrosis. The factors that regulate the development of mesenchymal progenitor cells in the bone marrow, their trafficking from the circulation into lesional tissue, and in situ into matrix-producing fibroblasts, are unknown. Epithelial and endothelial cells and fibroblasts can differentiate into smooth-muscle–like myofibroblasts characterized by prominent cytoskeleal structures containing alpha smooth muscle actin. While myofibroblasts can be transiently detected during normal wound healing, they persist in tissue during pathologic fibrogenesis, possibly due to resistance to apoptosis. Myofibroblasts contribute to scar formation via production of collagen and TGF-β, and contraction of the surrounding extracellular matrix.

Explanted fibroblasts display an abnormally activated phenotype in culture. Compared to normal fibroblasts, SSc fibroblasts have variably increased rates of collagen gene transcription and display smooth-muscle actin stress fibers. Furthermore, they show enhanced secretion of extracellular matrix molecules, cytokines, and growth factors; expression of chemokine receptors and cell surface adhesion molecules; resistance to apoptosis; spontaneously generate ROS; and autocrine TGF-β signaling. The abnormal "scleroderma phenotype" of these cells persists during their serial passage in vitro. Factors contributing to the autonomously activated phenotype include autocrine TGF-β stimulatory loops, hypoxia, deregulated microRNA expressions and other epigenetic modifications, and altered cell-matrix interaction. Global transcriptome analyses show differential expression of many extracellular matrix genes, including collagens, fibronectin, and fibrillins in SSc fibroblasts. A majority of the abnormally expressed genes could be linked to TGF-β responses, but other fibrogenic signaling pathways involving CTGF, endothelin-1m hypoxia, PDGF and Wnts are also operative in SSc.

PATHOLOGY

The distinguishing pathologic hallmark of SSc is the combination of widespread capillary loss and obliterative vasculopathy of small arteries and arterioles,

together with fibrosis in the skin and internal organs. In early disease, perivascular cellular infiltrates composed of CD4+ and CD8+ T lymphocytes, monocytes/macrophages, plasma cells, mast cells, and occasionally B cells may be detected in multiple organs prior to the appearance of fibrosis. The vascular lesion is characterized by intimal proliferation in the small and medium-sized arteries, resulting in luminal narrowing. Obliterative vasculopathy as a late finding is prominent in the heart, lungs, kidneys, and intestinal tract. Fibrosis is found in the skin, lungs, gastrointestinal tract, heart, tendon sheath, perifascicular tissue surrounding skeletal muscle, and some endocrine organs. In these tissues, accumulation of connective tissue composed of endothelin-1m collagens, fibronectin, proteoglycans, and other structural macromolecules progressively disrupts normal architecture, resulting in functional impairment of affected organs.

SKIN

In the skin, fibrosis causes dermal expansion and obliteration of the hair follicles, sweat glands, and other appendages **(Fig. 8-2*A*)**. Collagen fiber accumulation is most prominent in the reticular dermis, and the fibrotic process invades the subjacent adipose layer with entrapment of fat cells. The epidermis is atrophic, and the rete pegs are effaced.

LUNGS

Patchy infiltration of the alveolar walls with T lymphocytes, macrophages, and eosinophils occurs in early disease. With progression, interstitial fibrosis and vascular damage dominate the pathologic picture, often coexisting within the same lesions in patients with dcSSc. Pulmonary fibrosis is characterized by expansion of the alveolar interstitium, with accumulation of collagen and other connective tissue proteins. The most common histologic pattern in SSc is fibrotic nonspecific interstitial pneumonia **(Fig. 8-2*B*)**. Progressive thickening of the alveolar septae results in obliteration of the airspaces and honeycombing, as well as loss of pulmonary blood vessels. This process impairs gas exchange and contributes to worsening of pulmonary hypertension. Intimal thickening of the pulmonary arteries, best seen with elastin stain, underlies pulmonary hypertension **(Fig. 8-2*C*)** and, at autopsy, is often associated with multiple pulmonary emboli and evidence of myocardial fibrosis.

GASTROINTESTINAL TRACT

Pathologic changes can be found at any level from the mouth to the rectum. The lower esophagus is frequently involved, with prominent atrophy of the

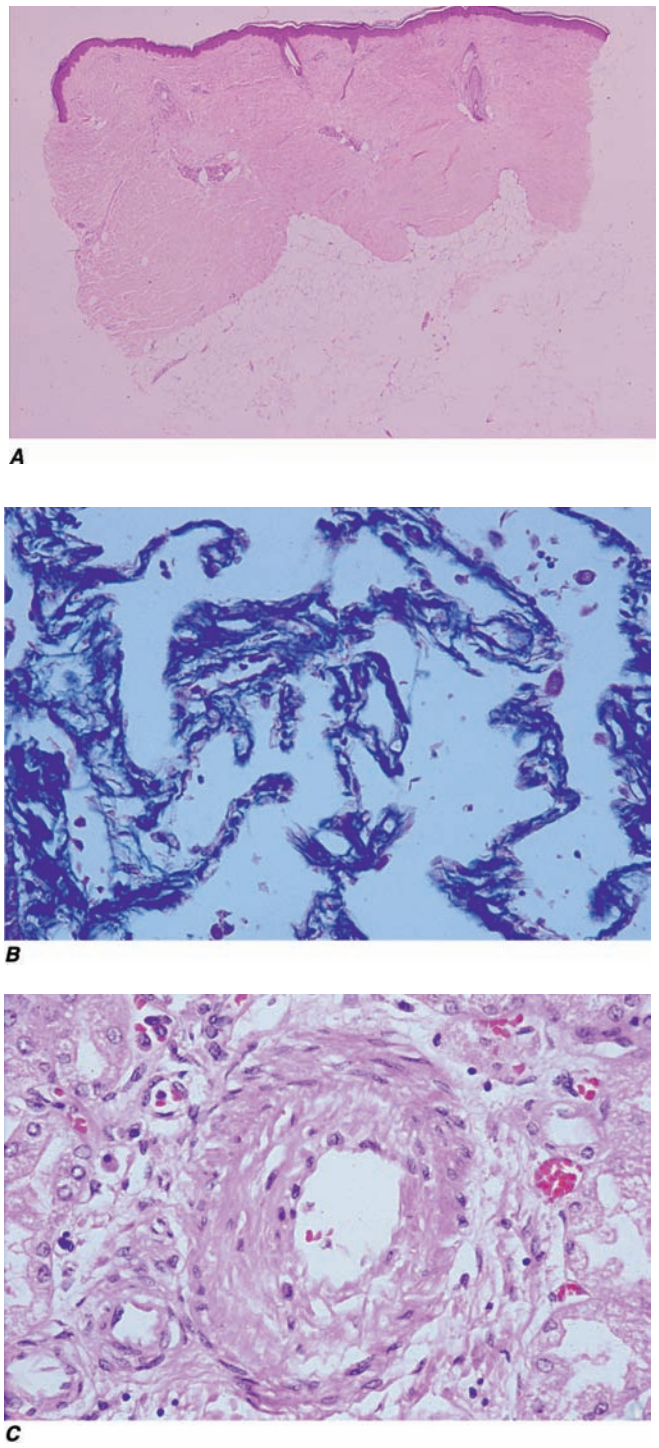


FIGURE 8-2

Pathologic findings in systemic sclerosis (SSc). *A.* Dermal sclerosis. The skin is thickened due to marked expansion of the dermis. Thick bundles of densely packed collagen replace skin appendages. ***B.*** Early interstitial lung disease. Diffuse fibrosis of the alveolar septae and a chronic inflammatory cell infiltrate. Trichrome stain. ***C.*** Pulmonary arterial obliterative vasculopathy. Striking intimal hyperplasia and narrowing of the lumen of a small pulmonary artery, with minimal interstitial fibrosis, in a patient with limited cutaneous SSc.

muscular layers; striated muscle in the upper third of the esophagus is generally spared. Characteristic vascular lesions are often present. Replacement of the normal intestinal tract architecture results in diminished peristaltic activity, with gastroesophageal reflux, dysmotility, and small-bowel obstruction. Chronic reflux is associated with esophageal inflammation, ulcerations, and stricture formation and may lead to Barrett's metaplasia.

KIDNEYS

In the kidneys, lesions in the interlobular and arcuate arteries predominate, whereas glomerulonephritis is rare. Chronic renal ischemia is associated with shrunken glomeruli. Patients with scleroderma renal crisis show dramatic changes in small renal arteries with reduplication of elastic lamina, marked intimal proliferation, and narrowing of the lumen, often accompanied by thrombosis and microangiopathic hemolysis.

HEART

The heart is frequently affected, with prominent involvement of the myocardium and pericardium. The characteristic arteriolar lesions are concentric intimal hypertrophy and luminal narrowing, accompanied by contraction band necrosis reflecting ischemia-reperfusion injury, and patchy myocardial fibrosis that may also affect the conduction system. Despite the prominent role of ischemia in SSc, the frequency of atherosclerotic coronary artery disease is comparable to the general population.

OTHER ORGANS

Synovitis may be found in early SSc; however, with progression of the disease, the synovium becomes fibrotic. Fibrosis of tendon sheaths and fascia produces palpable and sometimes audible tendon friction rubs. Inflammation, and, in later stages, atrophy and fibrosis of the muscles are common findings. Fibrosis of the thyroid gland and of the minor salivary glands may be seen.

CLINICAL FEATURES

OVERVIEW

Virtually every organ is affected in SSc **(Table 8-4)**. While there is a great deal of variability in the clinical manifestations from one patient to the next, patients can be classified into one of two major subsets based on the pattern of skin involvement (Table 8-2).

TABLE 8-4

INTERNAL ORGAN INVOLVEMENT: LIMITED CUTANEOUS AND DIFFUSE CUTANEOUS FORMS OF SYSTEMIC SCLEROSIS

FEATURES	LIMITED CUTANEOUS SSC (%)	DIFFUSE CUTANEOUS SSC (%)
Skin involvement	90*	100
Raynaud's phenomenon	99	98
Esophageal involvement	90	80
Pulmonary fibrosis	35	65
Pulmonary arterial hypertension	15	15
Myopathy	11	23
Cardiac involvement	9	12
Scleroderma renal crisis	2	15

*10% of lcSSc patients have SSc sine scleroderma.

Moreover, while dcSSc is associated with prominent and early internal organ involvement, lcSSc presents with long-standing Raynaud's phenomenon, indolent skin, limited internal organ involvement, and a better prognosis. While patient stratification into diffuse and limited cutaneous subsets is useful, disease expression is far more complex, and several distinct phenotypes exist within each subset. For example, 10–15% of patients with lcSSc develop severe pulmonary arterial hypertension without significant interstitial lung disease (ILD). Other patients have systemic features of SSc without appreciable skin involvement (SSc sine scleroderma). Unique clinical phenotypes of SSc associate with specific autoantibodies (Table 8-3). Patients with "overlap" have typical SSc features coexisting with clinical and laboratory evidence of another autoimmune disease such as polymyositis, Sjögren's syndrome, polyarthritis, autoimmune liver disease, or SLE.

The term *scleroderma* refers to localized scleroderma and is used to describe a group of localized skin disorders that primarily affect children (Table 8-1). In contrast to SSc, localized scleroderma is rarely associated with Raynaud's phenomenon or internal organ involvement. Morphea presents as solitary or multiple circular patches of thickened skin and, less commonly, widespread induration (generalized or pansclerotic morphea); the fingers are spared. Linear scleroderma—streaks of thickened skin, typically in one or both lower extremities—may affect the subcutaneous tissues with fibrosis and atrophy of supporting structures, muscle, and bone. In children, the growth of affected long bones can be retarded. When linear scleroderma lesions cross joints, significant contractures can develop.

INITIAL CLINICAL PRESENTATION

The initial presentation is quite different in the diffuse and the limited cutaneous forms of the disease. In patients with dcSSc, the interval between Raynaud's phenomenon and appearance of other manifestations is generally brief (weeks to months). Soft tissue swelling and intense pruritus are signs of the early inflammatory "edematous" phase of dcSSc. The fingers, hands, distal limbs, and face are usually affected first. Diffuse hyperpigmentation and carpal tunnel syndrome can occur. Arthralgias, muscle weakness and decreased joint mobility are common. During the ensuing weeks to months, the inflammatory edematous phase evolves into the "fibrotic" phase, with skin induration that is associated with loss of body hair, reduced production of skin oils, and a decline in sweating capacity. The subcutaneous tissue becomes affected, with fat atrophy and fibrosis of underlying fascia, muscle, and other soft tissue structures. Progressive flexion contractures of the fingers ensue. The wrists, elbows, shoulders, hip girdles, knees, and ankles become stiff due to fibrosis of the supporting joint structures. While advancing skin involvement is the most visible manifestation of early dcSSc, important internal organ involvement develops during this stage. The initial 4 years from disease onset is the period of rapidly evolving systemic involvement and greatest risk for pulmonary and renal damage. If organ failure does not occur during this period, the systemic process may stabilize.

Compared to dcSSc, the course of lcSSc is generally more indolent. The period between the onset of Raynaud's phenomenon and manifestations such as gastroesophageal reflux, telangiectasia, or calcinosis can be several years. Raynaud's phenomenon tends to be more severe than in dcSSc, and can be associated with critical ischemia, ulcerations, and autoamputation of the fingers. On the other hand, significant renal involvement and pulmonary fibrosis are uncommon in lcSSc patients. Cardiac involvement and isolated pulmonary arterial hypertension develop in 10–15%. Overlap of SSc with the sicca complex, polyarthritis, cutaneous vasculitis, and biliary cirrhosis is seen primarily in the lcSSc subset.

ORGAN INVOLVEMENT

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is an episodic vasoconstriction in the fingers and toes that occurs in virtually every patient with SSc. Vasoconstriction may also affect the tip of the nose and earlobes. Attacks are triggered by exposure to cold, a decrease in temperature, emotional stress, and vibration. Typical attacks start with pallor, followed by cyanosis of variable duration. Eventually erythema develops spontaneously or with rewarming of the digit. The progression of the three color phases reflects the underlying pathogenic mechanisms of vasoconstriction, ischemia, and reperfusion.

As much as 3–5% of the general population has Raynaud's phenomenon, and it is more frequent in women. In the absence of associated signs or symptoms of an underlying condition, Raynaud's phenomenon is classified as primary, and represents an exaggerated physiologic response to cold. Secondary Raynaud's phenomenon can occur as a complication of SSc and other connective tissue diseases, hematologic and endocrine conditions, and occupational disorders, and with the use of drugs such as the beta blocker atenolol and anticancer drugs such as cisplatin and bleomycin. Distinguishing primary versus secondary Raynaud's phenomenon can present a diagnostic challenge. The diagnosis of primary Raynaud's phenomenon is supported by the following: absence of an underlying cause on history and physical examination; a family history of Raynaud's phenomenon; absence of digital tissue necrosis, ulceration, or gangrene; and a negative test for antinuclear antibodies. Secondary Raynaud's phenomenon tends to develop at an older age (>30 years), is clinically more severe (episodes more frequent, prolonged, and painful), and is frequently associated with ischemic lesions and infarction in the digits **(Fig. 8-3)**. The cutaneous capillaries at the nail bed can be viewed under a drop of grade B immersion oil using a low-power stereoscopic microscope. Nailfold capillaroscopy can be helpful in the evaluation of Raynaud's phenomenon; patients with primary Raynaud's phenomenon have normal capillaries that appear as regularly spaced parallel vascular loops, whereas in SSc and other connective tissue diseases, nailfold capillaries



FIGURE 8-3
Digital necrosis. Sharply demarcated necrosis of the fingertip in a patient with limited cutaneous systemic sclerosis (SSc) associated with severe Raynaud's phenomenon.

are distorted with widened and irregular loops, dilated lumen, and areas of vascular "dropout." In SSc, abnormal vascular reactivity may involve multiple vascular beds, and cold-induced Raynaud's-like episodic vasospasm has been documented in the pulmonary, renal, gastrointestinal, and coronary circulations.

SKIN FEATURES

While early-stage SSc is associated with edematous skin changes, skin thickening is the hallmark that distinguishes SSc from other connective tissue diseases. The distribution of skin thickening is invariably symmetric and bilateral. It typically starts in the fingers, and then characteristically advances from distal to proximal extremities in an ascending fashion. The involved skin is firm, coarse, and thickened, and the extremities and trunk may be darkly pigmented. In some patients, diffuse tanning in the absence of sun exposure is a very early manifestation of skin involvement. In dark-skinned patients, vitiligo-like hypopigmentation may occur. Because pigment loss spares the perifollicular areas, the skin may have a "salt-and-pepper" appearance, most prominently on the scalp, upper back, and chest. Dermal sclerosis due to collagen accumulation causes obliteration of hair follicles, sweat glands, and eccrine and sebaceous glands, resulting in hair loss, decreased sweating, and dry skin. Transverse creases on the dorsum of the fingers disappear **(Fig. 8-4)**. Fixed flexion contractures of the fingers cause reduced hand mobility and lead to muscle atrophy. Skin thickening in combination with fibrosis of the subjacent tendons accounts for contractures of the wrists, elbows, and knees. Thick ridges at the neck due to firm adherence of skin to the underlying platysma muscle interfere with neck extension. The face assumes a characteristic "mauskopf" appearance with taut and shiny skin, loss of wrinkles, and occasionally an expressionless facies due to reduced mobility of the eyelids, cheeks, and mouth. Thinning of the lips with accentuation of the central incisor teeth and fine wrinkles (radial furrowing) around the mouth complete the picture. Reduced oral aperture (microstomia) interferes with eating and oral hygiene. The nose assumes a pinched, beak-like appearance.

In established SSc, the skin is firmly bound to the subcutaneous fat (tethering) and undergoes thinning and atrophy. Telangiectasia are dilated skin capillaries 2–20 mm in diameter frequently seen in lcSSc. These lesions, reminiscent of hereditary hemorrhagic telangiectasia, are prominent on the face, hands, lips, and oral mucosa **(Fig. 8-5)**. Breakdown of atrophic skin leads to chronic ulcerations at the extensor surfaces of the proximal interphalangeal joints, the volar pads of the fingertips, and bony prominences such as the elbows and malleoli. Ulcers are painful and may become secondarily infected, resulting in osteomyelitis. Healing of ischemic fingertip ulcerations leaves characteristic fixed digital "pits."



FIGURE 8-4
Sclerodactyly. Note skin induration on the fingers, and fixed flexion contractures at the proximal interphalangeal joints in a patient with limited cutaneous systemic sclerosis (SSc).



A



B

FIGURE 8-5
Cutaneous vascular changes. ***A.*** Capillary changes at the nailfold in a patient with limited cutaneous systemic sclerosis (lcSSc). ***B.*** Telangiectasia on the face.



FIGURE 8-6
Acro-osteolysis. Note dissolution of terminal phalanges in a patient with long-standing limited cutaneous systemic sclerosis (lcSSc) and Raynaud's phenomenon.

Loss of soft tissue at the fingertips due to ischemia is frequent and may be associated with striking resorption of the terminal phalanges (acro-osteolysis) **(Fig. 8-6)**.

Calcium deposits occur in the skin and soft tissues. Calcinosis cutis is most common in patients with lcSSc who are positive for anticentromere antibodies. The deposits, varying in size from tiny punctate lesions to large conglomerate masses, are composed of calcium hydroxyapatite crystals and can be readily visualized on plain x-rays. Frequent locations include the finger pads, palms, extensor surfaces of the forearms, and the olecranon and prepatellar bursae **(Fig. 8-7)**. Paraspinal calcifications may cause neurologic complications. Calcific deposits appears as persistent firm, nontender subcutaneous lumps. They may occasionally ulcerate through the overlying skin, producing drainage of chalky white material, pain, and local inflammation.



FIGURE 8-7
Calcinosis cutis. Note large calcific deposit breaking through the skin in a patient with limited cutaneous systemic sclerosis (lcSSc).

PULMONARY FEATURES

Pulmonary involvement can be documented in most patients with SSc and is now the leading cause of death. There are two main types of significant pulmonary involvement: ILD and PAH. Many patients with SSc develop some degree of both complications. Less frequent pulmonary manifestations of SSc include aspiration pneumonitis complicating gastroesophageal reflux, pulmonary hemorrhage due to endobronchial telangiectasia, obliterative bronchiolitis, pleural reactions, restrictive ventilatory defect due to chest wall fibrosis, spontaneous pneumothorax, and drug-induced lung toxicity. The incidence of lung cancer, particularly bronchioloalveolar carcinoma, may be increased.

Pulmonary involvement can remain asymptomatic until it is advanced. The most frequent presenting respiratory symptoms—exertional dyspnea, fatigue, and reduced exercise tolerance—are often subtle and slowly progressive. A chronic dry cough may be present. Physical examination may reveal "Velcro" crackles at the lung bases. Pulmonary function testing (PFT) is a sensitive method for detecting early pulmonary involvement. The most common abnormalities are reductions in forced vital capacity (FVC) or single breath diffusing capacity of the lung for carbon monoxide (DLCO). A reduction in DLCO that is significantly out of proportion to the reduction in FVC suggests pulmonary vascular disease, but may also be due to anemia. With exercise, patients show a decrease in PO_2.

Interstitial lung disease (ILD)

Some evidence of ILD can be found in up to 90% of patients with SSc at autopsy and 85% by thin-section high-resolution computed tomography (HRCT). ILD and pulmonary fibrosis cause restrictive pulmonary function defect with impaired gas exchange, characterized on PFT by decreased FVC and DLCO, but unaffected flow rates. Clinically significant ILD develops in 16–43% of patients with SSc; the frequency varies depending on the detection method used. Risk factors include male gender, African American race, diffuse skin involvement, severe gastroesophageal reflux, and the presence of topoisomerase-I autoantibodies, as well as a low FVC or DLCO at initial presentation. In patients who develop significant ILD, the most rapid progression in lung disease occurs early in the course of the disease (within the first 3 years), when the FVC can decline by 30% per year.

Chest radiography is useful for ruling out infection and other causes of pulmonary involvement, but compared to HRCT it is relatively insensitive for detection of early ILD. HRCT may show subpleural reticular linear opacities, predominantly in the lower lobes, even in asymptomatic patients **(Fig. 8-8)**. Additional findings include mediastinal lymphadenopathy, nodules, traction bronchiectasis and

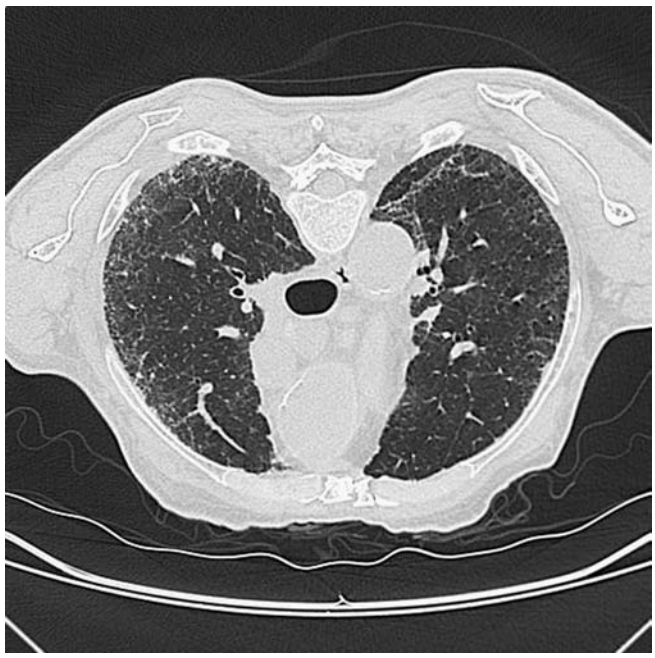


FIGURE 8-8

High-resolution CT scan of the lungs: interstitial lung disease. Note bilateral reticulonodular opacifications in a peripheral distribution in the lower lobes of the lungs in a patient with diffuse cutaneous systemic sclerosis (dcSSc).

in some cases, honeycomb cystic changes. Ground-glass opacification, alone or in combination with a reticular pattern, is seen in 50% of patients. Ground-glass opacification on HRCT is indicative of fine fibrosis, and does not identify alveolitis or predict rapid progression. The extent of lung disease on HRCT is a predictor of mortality in SSc. Bronchoalveolar lavage (BAL) can demonstrate inflammation in the lower respiratory tract and may be useful for ruling out infection., While an elevated proportion of neutrophils (>2%) and/or eosinophils (>3%) in the BAL fluid is correlated with more extensive lung disease on HRCT, and is associated with more rapid decline in FVC and reduced survival, BAL is not useful for identifying reversible alveolitis. Lung biopsy is indicated only in patients with atypical findings on chest radiographs and should be thoracoscopically guided. The histologic pattern on lung biopsy may be helpful in predicting the risk of progression of ILD. The most common pattern in SSc, nonspecific interstitial pneumonia, carries a better prognosis than usual interstitial pneumonia. Recent studies suggest that measurement of serum factors such as KL-6, a glycoprotein found in type II pneumocytes and alveolar macrophages, may have utility as biomarkers for the detection and serial monitoring of ILD in patients with SSc.

Pulmonary arterial hypertension (PAH)

PAH, defined as a mean pulmonary arterial pressure >25 mmHg with a pulmonary capillary wedge pressure <15 mmHg, is a major complication of SSc. Approximately 15% of SSc patients have PAH that can occur in association with ILD or as an isolated pulmonary abnormality. The natural history of SSc-associated PAH is variable, but in many patients it follows a downhill course with development of right heart failure and significant mortality. Risk factors for PAH include limited cutaneous disease with anticentromere antibodies, late age at disease onset, severe Raynaud's phenomenon, and the presence of antibodies to U1-RNP, U3-RNP (fibrillarin), and B23.

Patients with early PAH are generally asymptomatic. The initial symptom is typically exertional dyspnea and reduced exercise capacity. With progression, angina, exertional near-syncope, and symptoms and signs of right-sided heart failure appear. Physical examination shows tachypnea, a prominent pulmonic S_2 heart sound, palpable right ventricular heave, elevated jugular venous pressure, and dependent edema. Doppler echocardiography provides a noninvasive method for estimating the pulmonary arterial pressure is widely used to screen and for pulmonary hypertension. Echocardiographic estimates of pulmonary arterial systolic pressures exceeding 40 mmHg at rest suggest PAH. Pulmonary function testing may show a reduced DL_{CO} in isolation or combined with a restrictive pattern. Because echocardiography can result in over- or underestimation of pulmonary arterial pressures in SSc, right heart catheterization is always required to confirm the presence of PAH and accurately assess its severity, including the degree of right heart dysfunction. Serum levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP correlate with the presence and severity of PAH in SSc, as well as survival. Therefore, BNP measurements can be useful in screening SSc patients and in monitoring the response to treatment. The prognosis of PAH is determined by the degree of pulmonary arterial pressure elevation.

GASTROINTESTINAL INVOLVEMENT

The gastrointestinal tract is affected in up to 90% of SSc patients with both limited and diffuse cutaneous forms of the disease. The pathologic features of atrophy of smooth muscle, intact mucosa, and obliterative small-vessel vasculopathy are similar throughout the length of the gastrointestinal tract.

Upper gastrointestinal tract involvement

Oropharyngeal manifestations due to a combination of xerostomia, reduced oral aperture, periodontal disease and resorption of the mandibular condyles are frequent. The frenulum of the tongue may be shortened. Symptoms of gastroesophageal reflux disease (GERD) develop early. Most patients have heartburn, regurgitation, and dysphagia. A combination of reduced lower esophageal

sphincter pressure resulting in gastroesophageal reflux, impaired esophageal clearance of refluxed gastric contents due to diminished motility in the distal two-thirds of the esophagus, and delayed gastric emptying accounts for GERD. Chest CT scan characteristically shows a dilated esophagus with intraluminal air. Severe erosive esophagitis may be found on endoscopy in patients with minimal symptoms. Endoscopy may be necessary to rule out opportunistic infections with candida, herpes virus, and cytomegalovirus. Esophageal strictures and Barrett's esophagus may complicate chronic GERD. Because Barrett's esophagus is associated with an increased risk of adenocarcinoma, SSc patients with this lesion need to undergo periodic endoscopy and biopsy. Extraesophageal manifestations of GERD such as hoarseness and chronic cough may occur. Aspiration pneumonitis also may occur, aggravating underlying ILD.

Gastroparesis with early satiety, abdominal distention, and aggravated reflux symptoms is common. The presence and severity of gastroparesis can be assessed by radionuclide gastric emptying studies. Gastric antral vascular ectasia (GAVE) in the antrum may occur. These subepithelial lesions, reflecting the diffuse small-vessel vasculopathy of SSc, are described as "watermelon stomach" due to their endoscopic appearance. Patients with GAVE can have recurrent episodes of gastrointestinal bleeding, resulting in chronic unexplained anemia. Manometric testing shows abnormalities in the upper small intestines of most patients with SSc.

Lower gastrointestinal tract involvement

Impaired intestinal motility may result in malabsorption and chronic diarrhea secondary to bacterial overgrowth. Fat and protein malabsorption and B_{12} and vitamin D deficiency ensue, sometimes culminating in severe malnutrition. Disturbed intestinal motor function can also cause intestinal pseudoobstruction, with symptoms of nausea and abdominal distension that are indistinguishable from those of delayed gastric emptying. Patients present with recurrent episodes of acute abdominal pain, nausea, and vomiting. Radiographic studies show acute intestinal obstruction, and the major diagnostic challenge is to differentiate pseudoobstruction, which responds to supportive care and intravenous nutritional supplementation, from mechanical obstruction. Colonic involvement may cause severe constipation, fecal incontinence, gastrointestinal bleeding from telangiectasia, and rectal prolapse. In late-stage SSc, wide-mouth sacculations or diverticula occur in the colon, occasionally causing perforation and bleeding. An occasional radiologic finding is pneumatosis cystoides intestinalis due to air trapping in the bowel wall that may rarely rupture and cause benign pneumoperitoneum. Although the liver is rarely affected, primary biliary cirrhosis may coexist with SSc.

RENAL INVOLVEMENT: SCLERODERMA RENAL CRISIS

Scleroderma renal crisis, the most dreaded complication of SSc, occurs in 10–15% of patients, and almost always within 4 years of the onset of the disease. Prior to the advent of ACE inhibitors, short-term survival in scleroderma renal crisis was <10%. The pathogenesis involves obliterative vasculopathy and luminal narrowing of the renal arcuate and interlobular arteries. Progressive reduction in renal blood flow, aggravated by vasospasm, leads to juxtaglomerular hyperplasia, increased renin secretion, and activation of angiotensin, with further renal vasoconstriction resulting in a vicious cycle that culminates in malignant hypertension. Risk factors for scleroderma renal crisis include African American race, male gender, diffuse cutaneous SSc with extensive and progressive skin involvement, and autoantibodies to RNA polymerases I and III. Palpable tendon friction rubs, pericardial effusion, new unexplained anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis. High-risk patients with early SSc should be counseled to check their blood pressure daily. Patients with lcSSc infrequently develop scleroderma renal crisis. Because there is an association between glucocorticoid use and the onset of scleroderma renal crisis, prednisone should be used in high-risk SSc patients only when absolutely required, and at low doses (<10 mg/d).

Patients characteristically present with accelerated hypertension and progressive renal insufficiency. However, in approximately 10% of patients, blood pressure remains normal. Normotensive renal crisis is generally associated with a poor outcome. Headache, blurred vision, and chest pain may accompany elevation of blood pressure. Urinalysis typically shows mild proteinuria, granular casts, and microscopic hematuria; thrombocytopenia and microangiopathic hemolysis with fragmented red blood cells can be seen. Progressive oliguric renal failure over several days generally follows. In some cases, scleroderma renal crisis is misdiagnosed as thrombotic thrombocytopenic purpura. The value of kidney biopsy in this setting is uncertain. Oliguria or a creatinine >3 mg/dL at presentation predicts poor outcome, with permanent hemodialysis and high mortality. Prompt aggressive intervention with short-acting ACE inhibitors to achieve adequate blood pressure control before the onset of renal failure results in improved prognosis. In contrast, there is no evidence to support the practice of "prophylactic" use of ACE inhibitors in normotensive SSc patients. Rarely, crescentic glomerulonephritis occurs in the setting of SSc.

CARDIAC INVOLVEMENT

Although cardiac involvement is often clinically silent, it is frequently detected when sensitive diagnostic tools

are used. Cardiac disease occurs more frequently in patients with dcSSc than in those with lcSSc, and generally develops within 3 years of the onset of skin thickening. Clinically evident cardiac involvement in SSc is a poor prognostic factor. The endocardium, myocardium, and pericardium may be affected separately or together. Manifestations include pericardial effusions, atrial and ventricular tachycardias, conduction abnormalities, valvular regurgitation, hypertrophy, and heart failure. Systemic and pulmonary hypertension and lung and renal involvement may also impact on the heart. Despite the presence of widespread obliterative vasculopathy, the frequency of clinical or pathologic epicardial coronary artery disease in SSc is not increased. While conventional echocardiography has low sensitivity for detecting SSc preclinical heart involvement, newer modalities such as tissue Doppler echocardiography (TDE) and cardiac magnetic resonance imaging (MRI) reveal a high prevalence of abnormal myocardial function. Thallium perfusion studies document abnormal cardiac perfusion in a majority of patients. The serum level of N-terminal pro-brain natriuretic peptide (NT-pro-BNP), a ventricular hormone, is a sensitive and specific diagnostic marker for increased pulmonary artery pressure in SSc, but may also have utility as a marker of primary cardiac involvement. Myocarditis can occur in association with inflammatory polymyositis, and can be diagnosed using cardiac MRI. Pericardial effusions occur in over 15% of patients and, rarely, may cause tamponade.

MUSCULOSKELETAL COMPLICATIONS

Carpal tunnel syndrome occurs frequently and may be a presenting manifestation of SSc. Generalized arthralgia and stiffness are prominent in early disease. Joint mobility is progressively impaired, especially in patients with dcSSc. Most commonly affected are the hands. Contractures develop at the proximal interphalangeal joints and wrists. In patients with dcSSc, large joint contractures can be accompanied by tendon friction rubs characterized by leathery crepitation that can be heard or palpated upon passive movement. Tendon rubs are due to extensive fibrosis and adhesion of the tendon sheaths and fascial planes at the affected joint. Movement at the elbows, shoulders, and knees is frequently reduced. True joint inflammation is uncommon; however, occasional patients develop erosive polyarthritis in the hands. Muscle weakness is common, and may indicate deconditioning, disuse atrophy, and malnutrition. Less commonly, inflammatory myositis indistinguishable from idiopathic polymyositis may occur. A chronic noninflammatory myopathy characterized by atrophy and fibrosis in the absence of elevated muscle enzyme levels can be seen in late-stage SSc. Bone resorption occurs most commonly in the terminal phalanges, where it causes loss of the distal tufts (acro-osteolysis) (Fig. 8-5). Resorption of the mandibular condyles can lead to bite difficulties. Osteolysis can also affect the ribs and distal clavicles.

OTHER DISEASE MANIFESTATIONS

Many SSc patients develop dry eyes and dry mouth (sicca complex). Biopsy of the minor salivary glands shows fibrosis rather than focal lymphocytic infiltration characteristic of primary Sjögren's syndrome (Chap. 9). Hypothyroidism is common and generally due to fibrosis of the thyroid gland. Whereas the central nervous system is generally spared in SSc, sensory trigeminal neuropathy due to fibrosis or vasculopathy can occur, presenting with gradual onset of pain and numbness. Pregnancy in women with SSc is associated with an increased rate of adverse fetal outcomes. Furthermore, cardiopulmonary involvement may worsen during pregnancy, and new onset of scleroderma renal crisis has been described. Erectile dysfunction is frequent in men with SSc and may be the initial disease manifestation. Inability to attain or maintain penile erection is due to vascular insufficiency and fibrosis. The risk of certain malignancies is increased in SSc. Some studies have indicated that cancers of the lung, tongue, and breast occur more frequently in patients with SSc. Barrett's metaplasia is associated with increased risk for adenocarcinoma of the esophagus.

LABORATORY FEATURES

A mild normocytic or microcytic anemia due to chronic inflammation is frequent in patients with SSc. Iron deficiency anemia may indicate gastrointestinal bleeding caused by GAVE or chronic esophagitis. Macrocytic anemia, indicating a maturation disorder, may be caused by folate and vitamin B_{12} deficiency due to small bowel bacterial overgrowth and malabsorption, or by drugs such as methotrexate or alkylating agents. Microangiopathic hemolytic anemia, caused by mechanical trauma and fragmentation of red blood cells during their passage through microvessels coated with fibrin or platelet thrombi, is a hallmark of scleroderma renal crisis. Thrombocytopenia and leukopenia generally indicate drug toxicity. In contrast to other connective tissue diseases, the erythrocyte sedimentation rate (ESR) is generally normal; an elevation may signal coexisting myositis or malignancy.

Antinuclear autoantibodies are present in almost all patients with SSc and can be detected at disease onset. Autoantibodies against topoisomerase-I (Scl-70) and centromere are specific for SSc and are mutually exclusive. Topoisomerase-I antibodies are detected in 31% of patients with dcSSc, but in only 13% of patients with lcSSc; conversely, anticentromere antibodies are detected in 38% of patients with lcSSc, but in only 2% of patients with dcSSc. Anticentromere antibodies are

commonly associated with lcSSc and PAH, and only rarely with cardiac or renal involvement or significant ILD. Topoisomerase-I-positive patients have reduced survival compared to those without this antibody; whereas anticentromere antibody-positive patients have improved survival compared to those without this antibody. Nucleolar immunofluorescence pattern on serologic testing reflects antibodies to U3-RNP (fibrillarin), Th/To, or PM/Scl, whereas a speckled immunofluorescence pattern indicates antibodies to RNA polymerase III. Although antibodies to β2GPI occur in antiphospholipid antibody syndrome and are not specific for SSc, their presence in SSc is associated with an increased risk of ischemic lesions in the fingers. No direct pathogenic role has been firmly established for any of the SSc-associated autoantibodies; however, antibody titers can correlate with disease severity and fluctuate with disease activity.

DIAGNOSIS

The diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. The presence of skin induration, with a characteristic symmetric distribution pattern associated with typical visceral organ manifestations, establishes the diagnosis with a high degree of certainty. While the conditions listed in Table 8-1 can be associated with skin induration, the distribution pattern of skin lesions, together with the absence of Raynaud's phenomenon or typical visceral organ manifestations or SSc-specific autoantibodies, differentiates these conditions from SSc. Occasionally, full-thickness biopsy of the skin is required for establishing the diagnosis of scleredema, scleromyxedema, or nephrogenic systemic fibrosis. In lcSSc a history of antecedent Raynaud's phenomenon and gastroesophageal reflux symptoms, coupled with the presence of sclerodactyly and capillary changes on nailfold capillaroscopy, often in combinations with telangiectasia and calcinosis cutis, helps to establish the diagnosis. The finding of digital tip pitting scars and radiologic evidence of pulmonary fibrosis in the lower lobes are particularly helpful diagnostically. Primary Raynaud's phenomenon is a common benign condition that must be differentiated from early or limited SSc. Nailfold microscopy is particularly helpful in this situation, because in primary Raynaud's phenomenon the nailfold capillaries are normal, whereas in SSc capillary abnormalities, as well as serum autoantibodies can be detected even before other disease manifestations.

Establishing the diagnosis of SSc in early disease may be a challenge. In dcSSc, initial symptoms are often nonspecific and relate to inflammation. Patients complain of fatigue, swelling, aching, and stiffness, and Raynaud's phenomenon may initially be absent. Physical examination may reveal diffuse upper extremity edema and puffy fingers. Patients at this stage are sometimes diagnosed as early rheumatoid arthritis, systemic lupus erythematosus, myositis, or, most commonly, undifferentiated connective tissue disease. Within weeks to months, Raynaud's phenomenon and characteristic clinical features appear accompanied by advancing induration of the skin. The presence of antinuclear and SSc-specific autoantibodies provides a high degree of diagnostic specificity. Raynaud's phenomenon with fingertip ulcerations or other evidence of digital ischemia, coupled with telangiectasia, distal esophageal dysmotility, unexplained ILD or PAH, or accelerated hypertension with renal failure in the absence of skin induration, suggests the diagnosis of SSc sine scleroderma. These patients may have anticentromere antibodies.

TREATMENT Systemic Sclerosis

OVERVIEW To date, no therapy has been shown to significantly alter the natural history of SSc. In contrast, multiple interventions are highly effective in alleviating the symptoms and in slowing the progression of the cumulative organ damage. A significant reduction in disease-related mortality has been noted during the past 25 years. Because of the marked heterogeneity in clinical presentations, patients need careful investigation at baseline, and evaluation and treatment approaches must be individually tailored according to each patient's unique needs. Optimal management incorporates the following principles: prompt and accurate diagnosis; classification and risk stratification based on clinical and laboratory evaluation; early recognition of organ-based complications and assessment of their extent, severity, and likelihood of deterioration; regular monitoring for progression, disease activity, and response to therapy; and continuing patient education. In order to minimize irreversible organ damage, the management of life-threatening complications must be proactive, with regular screening and initiation of appropriate intervention at the earliest possible opportunity. In light of the complex, multisystemic nature of the disease, an integrated team-based approach is optimal. Most patients are treated with combinations of drugs that act upon different aspects of the disease. Patients should become familiar with the spectrum of potential complications, have an understanding of the therapeutic options and natural history of the disease, and be empowered to partner with their physicians. This typically requires a long-term relationship between patient and physician, with ongoing counseling and encouragement.

DISEASE-MODIFYING THERAPY: IMMUNOSUPPRESSIVE AGENTS Immunosuppressive agents effective in other connective tissue diseases have generally shown modest or no benefit in the treatment of SSc. Glucocorticoids may be useful for alleviating

stiffness and aching in early-stage dcSSc, but do not influence the progression of skin or internal organ involvement. Furthermore, their use in high doses is associated with an increased risk of scleroderma renal crisis. Therefore, glucocorticoids should be avoided if possible; when absolutely necessary, they should be given at the lowest dose possible and for brief periods only. The use of cyclophosphamide has been extensively studied in light of its efficacy in the treatment of vasculitis (Chap. 11), systemic lupus erythematosus (Chap. 4), and other autoimmune diseases (Chap. 3).

Cyclophosphamide has been evaluated in the treatment of SSc in retrospective and prospective controlled clinical trials. Both oral and intermittent intravenous cyclophosphamide were shown to reduce the progression of ILD in SSc patients with early symptomatic disease, with stabilization, and, rarely, modest improvement of pulmonary function and HRCT after 1 year of treatment. Improvement in respiratory symptoms and the extent of skin induration was also noted. The beneficial effect of cyclophosphamide on lung function wanes upon discontinuation of therapy. The benefits of cyclophosphamide need to be balanced against its potential toxicity, including bone marrow suppression, opportunistic infections, hemorrhagic cystitis and bladder cancer, premature ovarian failure, and late secondary malignancies.

In small clinical trials in SSc, methotrexate treatment was associated with a modest improvement in skin scores. Mycophenolate mofetil treatment was associated with improved skin induration in uncontrolled studies and was generally well tolerated. The use of immunomodulatory agents such as cyclosporine, azathioprine, rituximab, extracorporeal photophoresis, imatinib, thalidomide, or rapamycin for the treatment of SSc is currently not well supported by the literature. Immune ablation using high-dose chemotherapy with or without irradiation, followed by autologous stem cell reconstitution, is undergoing evaluation in randomized clinical trials in SSc. In light of its potential morbidity and mortality, as well as cost, autologous stem cell transplantation in SSc is still considered experimental.

Anti-Fibrotic Therapy Because widespread tissue fibrosis causes progressive organ damage in dcSSc, drugs that interfere with the fibrotic process represent a rational approach to therapy. D-Penicillamine has been extensively used as an antifibrotic agent. Retrospective studies in SSc indicated that D-penicillamine stabilized and improved skin induration, prevented new internal organ involvement, and improved survival. However, a randomized controlled clinical trial in early active SSc found no difference in the extent of skin involvement between patients treated with standard-dose (750 mg/d) or very low-dose (125 mg every other day) D-penicillamine. Minocycline, recombinant relaxin, interferon (INF)-γ, and inhibitors of tumor necrosis factor have failed to show meaningful clinical benefit in SSc.

Vascular Therapy The goal of vascular therapy is to control Raynaud's phenomenon, prevent the development and enhance the healing of ischemic complications, and slow the progression of obliterative vasculopathy. Patients with Raynaud's phenomenon should dress warmly, minimize cold exposure or stress, and avoid drugs that could precipitate or exacerbate vasospastic episodes. Some patients may respond to biofeedback therapy. Calcium channel blockers such as nifedipine or diltiazem are commonly used but show only moderate benefit, and their use is often limited by side effects (palpitations, dependent edema, lightheadedness). While ACE inhibitors do not reduce the frequency or severity of episodes, angiotensin II receptor blockers such as losartan are effective and generally well tolerated. Some patients with Raynaud's phenomenon may require α_1-adrenergic receptor blockers (e.g., prazosin), 5-phosphodiesterase inhibitors (e.g., sildenafil), serotonin reuptake inhibitors (e.g., fluoxetine), topical nitroglycerine, and intravenous prostaglandins. Low-dose aspirin and dipyridamole prevent platelet aggregation and may have a role as adjunctive agents. In patients with ischemic finger ulcerations, the endothelin-1 receptor antagonist bosentan reduces the development of new ulcers. Digital sympathectomy and local injections of botulinum type A (botox) into the digits are options in some patients with severe Raynaud's phenomenon associated with ischemia. Empirical long-term therapy with statins and antioxidants may delay the progression of vascular damage and obliteration. The use of calcium channel blockers has been associated with improved cardiac perfusion and cardiac function in SSc patients with cardiac involvement.

TREATMENT OF GASTROINTESTINAL COMPLICATIONS Because gastroesophageal reflux is very common, all patients with SSc should be treated for this complication. Significant reflux may occur in the absence of symptoms. Patients should be instructed to elevate the head of the bed and eat frequent small meals. Proton pump inhibitors reduce acid reflux and may need to be given in relatively high doses. Recurrent gastrointestinal bleeding from vascular ectasia in the gastric antrum (watermelon stomach) is amenable to treatment with laser photocoagulation. Bacterial overgrowth due to small-bowel dysmotility causes abdominal bloating and diarrhea and may lead to malabsorption and severe malnutrition. Treatment with short courses of rotating broad-spectrum antibiotics such as metronidazole, erythromycin, and tetracycline can eradicate bacterial overgrowth. Parenteral hyperalimentation is indicated if malnutrition develops. Chronic hypomotility of the small bowel may respond to octreotide.

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH) Because PAH is asymptomatic until it is advanced, patients with SSc should be screened for the presence of PAH on a regular basis. When PAH is symptomatic, treatment should be started with an oral endothelin-1 receptor antagonist or a phosphodiesterase inhibitor such as sildenafil. Patients may also require diuretics, oral anticoagulation, and digoxin when appropriate. If hypoxemia is documented, supplemental oxygen should be given by nasal cannula in order to avoid hypoxia-induced secondary pulmonary vasoconstriction. Inhibitors of phosphodiesterase type 5 (e.g., sildenafil) have been shown to have short-term efficacy in PAH and may be used in combination with bosentan. Prostacyclin analogues such as epoprostenol or treprostinil can be administered intravenously or by continuous subcutaneous infusion, or frequent inhalations via nebulizer. Lung transplantation remains an option for patients with SSc-associated PAH who fail medical therapy.

TREATMENT OF RENAL CRISIS Scleroderma renal crisis is a medical emergency because the outcome is largely determined by the extent of renal damage present at the time that aggressive therapy is initiated. Prompt recognition of impending or early scleroderma renal crisis is therefore essential, and efforts should be made to avoid its occurrence. High risk patients with early SSc and extensive and progressive skin involvement should be instructed to monitor their blood pressure daily and report significant alterations immediately. Potentially nephrotoxic drugs should be avoided, and glucocorticoids used only when absolutely necessary, and at low doses. When scleroderma renal crisis occurs, treatment should be started promptly with short-acting ACE inhibitors, with the goal of achieving rapid normalization of the blood pressure. Kidney biopsy is rarely useful in this setting. Up to two-thirds of patients require dialysis. However, substantial renal recovery can occur following renal crisis, and up to one-half of the patients may be able to discontinue dialysis. Kidney transplantation is appropriate for patients who are unable to discontinue dialysis after 2 years. Survival of SSc patients with with renal transplantation is comparable to that in other connective tissue diseases, and recurrence of renal crisis is rare.

SKIN CARE Because skin involvement in SSc is never life-threatening, and it stabilizes, and may even regress spontaneously over time, the overall management of the disease should not be dictated by its cutaneous manifestations. The inflammatory symptoms of early skin involvement can be effectively controlled with systemic antihistamines and cautious and short-term use of low-dose glucocorticoids (<5 mg/d of prednisone). Retrospective studies have shown that D-penicillamine reduced the extent and progression of skin induration; however, these benefits could not be substantiated in a controlled prospective trial. Cyclophosphamide and methotrexate have also been shown to have modest effects on skin induration. Because induration is associated with dryness, patients should use hydrophilic ointments and bath oils. Regular skin massage is helpful. Telangiectasia may present a cosmetic problem, especially when they occur on the face. Treatment with pulsed dye laser may have short-term benefit. Fingertip ulcerations should be protected by occlusive dressing to promote healing and prevent infection. Infected skin ulcers are treated with topical antibiotics. Surgical debridement may be indicated. No therapy has been shown to be effective in preventing the formation of calcific soft tissue deposits or in promoting their dissolution.

COURSE

The natural history of SSc is highly variable and difficult to predict, especially in early stages when the specific disease subset—diffuse or limited cutaneous form—is not clear. Patient with dcSSc have a more rapidly progressive disease and worse prognosis than those with lcSSc.

In dcSSc, early inflammatory symptoms such as fatigue, edema, arthralgia, and pruritus tend to subside 2–4 years after the onset of disease, and the extent of skin thickening reaches a plateau after which it generally shows slow regression. It is during the early edematous stage, generally lasting <3 years, that visceral organ involvement develops and progresses. While existing visceral organ involvement, such as pulmonary fibrosis, may continue to progress, new organ involvement is rare after the skin involvement reaches its peak. Scleroderma renal crisis almost invariably occurs within the first 4 years of disease. In dcSSc patients with late-stage disease (>6 years), the skin is usually soft and atrophic. Skin regression characteristically occurs in an order that is the reverse of initial involvement, with softening on the trunks followed by proximal and then distal extremities. Sclerodactyly and finger contractures generally persist. Cutaneous telangiectasia and calcinosis are common, making it difficult to differentiate late-stage dcSSc from lcSSc. Relapse or recurrence of skin thickening after the peak of skin involvement has been reached is rare. Patients with lcSSc follow a clinical course that is markedly different than that of dcSSc. In this subset of SSc, Raynaud's phenomenon typically precedes other disease manifestations by years or even decades. Visceral organ complications such as PAH and ILD generally develop late and tend to be slowly progressive.

PROGNOSIS

SSc confers a substantial increase in the risk of premature death, with age- and gender-adjusted mortality rates that are fivefold to eightfold higher compared to the general population. In one population-based study of SSc patients with all forms of the disease, the median survival was 11 years. In patients with dcSSc, 5- and 10-year survivals are 70% and 55%, respectively, whereas in patients with lcSSc, 5- and 10-year survivals are 90% and 75%, respectively. The prognosis of SSc correlates with the extent of skin involvement, which itself is a surrogate for visceral organ involvement. Major causes of death are PAH, pulmonary fibrosis, gastrointestinal involvement, and cardiac disease. Scleroderma renal crisis is associated with a 30% 3-year mortality. Lung cancer and excess cardiovascular deaths also contribute to increased mortality. Markers of worse prognosis include male gender, African American race, older age of disease onset, extensive skin thickening with truncal involvement, evidence of significant or progressive visceral organ involvement, and the presence of anti-topoisomerase-I and anti-RNA polymerase III antibodies. Additional predictors of increased mortality at initial evaluation include an elevated ESR, anemia, and proteinuria. In one study, SSc patients with extensive skin involvement, lung vital capacity <55% predicted, significant gastrointestinal involvement (pseudoobstruction or malabsorption), evidence of cardiac involvement (arrhythmias or congestive heart failure), or scleroderma renal crisis had a cumulative 9-year survival <40%. The severity of PAH is itself strongly associated with mortality, and SSc patients who had a mean pulmonary arterial pressure ≥45 mmHg had a 33% 3-year survival. The advent of ACE inhibitor therapy for scleroderma renal crisis had a dramatic impact on survival, increasing from a <10% 1-year survival in the pre-ACE inhibitor era to a >70% 3-year survival at the present time.

MIXED CONNECTIVE TISSUE DISEASE

Patients who have lcSSc coexisting with features of SLE, polymyositis, and rheumatoid arthritis may have mixed connective tissue disease (MCTD). This overlap syndrome is generally associated with the presence of high titers of autoantibodies to U1-RNP. The characteristic initial presentation is Raynaud's phenomenon associated with puffy fingers and myalgia. Gradually, lcSSc features of sclerodactyly, calcinosis, and cutaneous telangiectasia develop. Skin rashes suggestive of systemic lupus erythematosus (malar rash, photosensitivity) or of dermatomyositis (heliotrope rash on the eyelids, erythematous rash on the knuckles) occur. Arthralgia is common, and some patients develop erosive polyarthritis. Pulmonary fibrosis and isolated or secondary PAH may develop. Other manifestations include esophageal dysmotility, pericarditis, Sjögren's syndrome, and renal disease, especially membranous glomerulonephritis. Laboratory evaluation indicates features of inflammation with elevated ESR and hypergammaglobulinemia. While anti-U1RNP antibodies are detected in the serum in high titers, SSc-specific autoantibodies are not found. In contrast to SSc, patients with MCTD often show a good response to treatment with glucocorticoids, and the long-term prognosis is better than that of SSc. Whether MCTD is a truly distinct entity or is, rather, a subset of SLE or SSc remains controversial.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis is a rare idiopathic disorder associated with induration of the skin that generally develops rapidly. Adults are primarily affected. The skin has a coarse cobblestone "peau d'orange" appearance. In contrast to SSc, internal organ involvement is rare, and Raynaud's phenomenon and SSc-associated autoantibodies are absent. Furthermore, skin involvement spares the fingers. Full-thickness excisional biopsy of the lesional skin reveals fibrosis of the subcutaneous fascia, and is generally required for diagnosis. Inflammation and eosinophil infiltration in the fascia are variably present. In the acute phase of the illness, peripheral blood eosinophilia may be prominent. MRI appears to be a sensitive tool for the diagnosis of eosinophilic fasciitis. In some patients, eosinophilic fasciitis occurs in association with, or preceding, myelodysplastic syndromes or multiple myeloma. Treatment with glucocorticoids leads to prompt resolution of the eosinophilia. In contrast, skin changes generally show slow and variable improvement. The prognosis of patients with eosinophilic fasciitis is good.

CHAPTER 9

SJÖGREN'S SYNDROME

Haralampos M. Moutsopoulos ■ Athanasios G. Tzioufas

DEFINITION, INCIDENCE, AND PREVALENCE

Sjögren's syndrome is a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes. Approximately one-third of patients present with systemic manifestations; a small but significant number of patients may develop malignant lymphoma. The disease presents alone (primary Sjögren's syndrome) or in association with other autoimmune rheumatic diseases (secondary Sjögren's syndrome) **(Table 9-1)**.

Middle-aged women (female-to-male ratio, 9:1) are primarily affected, although it may occur in all ages, including childhood. The prevalence of primary Sjögren's syndrome is approximately 0.5–1%, while 30% of patients with autoimmune rheumatic diseases suffer from secondary Sjögren's syndrome.

PATHOGENESIS

Sjögren's syndrome is characterized by both lymphocytic infiltration of the exocrine glands and B lymphocyte hyperreactivity. An oligomonoclonal B cell process, which is characterized by cryoprecipitable monoclonal immunoglobulins (IgMκ) with rheumatoid factor activity, is evident in up to 25% of patients.

Sera of patients with Sjögren's syndrome often contain autoantibodies directed against non-organ-specific antigens such as immunoglobulins (rheumatoid factors) and extractable nuclear and cytoplasmic antigens (Ro/SS-A, La/SS-B). Ro/SS-A autoantigen consists of two polypeptides (52 and 60 kDa) in conjunction with cytoplasmic RNAs, whereas the 48-kDa La/SS-B protein is bound to RNA III polymerase transcripts. Autoantibodies to Ro/SS-A and La/SS-B antigens are usually detected at the time of diagnosis and are associated with earlier disease onset, longer disease duration, salivary gland enlargement, more severe lymphocytic infiltration of minor salivary glands, and certain extraglandular manifestations. Antibodies to α-fodrin (120 kDa), a salivary gland–specific protein, as well as muscarinic receptor 3 (M3R) also have been found in sera of patients with Sjögren's syndrome. The major infiltrating cells in the affected exocrine glands are activated T and B lymphocytes. T cells predominate in mild lesions, whereas B-cells in more severe lesions. T regulatory cells also have been detected. Macrophages and dendritic cells also are found. The number of interleukin (IL)-18 positive macrophages has been shown to correlate with parotid gland enlargement and low levels of the C4 component of complement, both adverse predictors for lymphoma development. Glandular epithelial cells undergo apoptotic death by signals provided from T cells. Infiltrating lymphocytes not only provide apoptotic messages to epithelial cells but also tend to be resistant to apoptosis. Ductal and acinar epithelial cells appear to play a significant role in the initiation and perpetuation of the autoimmune injury. They express class II major histocompatibility complex (MHC), costimulatory molecules, and intracellular autoantigens expressed on cell membranes, thus being able to provide signals essential for lymphocytic activation. Finally, they

TABLE 9-1

ASSOCIATION OF SJÖGREN'S SYNDROME WITH OTHER AUTOIMMUNE DISEASES
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Mixed connective tissue disease
Primary biliary cirrhosis
Vasculitis
Chronic active hepatitis

inappropriately produce proinflammatory cytokines and lymphoattractant chemokines necessary for sustaining the autoimmune lesion and progressing to more sophisticated ectopic germinal center formation, that occurs in one-fifth of patients. They also express functional receptors of innate immunity, particularly TLR 3, 7, and 9, that may account for the perpetuation of the autoimmune response. Similar to T cells, CD40+ B cells also have a tendency to be resistant to apoptosis. B-cell activating factor (BAFF) has been found to be elevated in patients with Sjögren's syndrome, especially those with hypergammaglobulinemia, and probably accounts for this antiapoptotic effect. Glandular epithelial cells seem to have an active role in the production of BAFF, since it may be expressed and secreted after stimulation with type I interferon, as well as with viral or synthetic dsRNA. The triggering factor for epithelial activation appears to be a persistent enteroviral infection (possibly by coxsackievirus strains).

A defect in cholinergic activity mediated through the M3 receptor and redistribution of the water-channel protein aquaporin-5, both leading to neuroepithelial dysfunction and diminished glandular secretions, have been proposed.

Molecular analysis of human leukocyte antigen (HLA) class II genes has revealed that patients with Sjögren's syndrome, regardless of their ethnic origin, are highly associated with the HLA DQA1* 0501 allele. Recent genome-wide association studies, disclosed increased prevalence of single nucleotide polymorphisms in genes of IRF-5 and STAT-4, participating in the activation of the type I interferon pathway.

CLINICAL MANIFESTATIONS

The majority of Sjögren's syndrome patients have symptoms related to diminished lacrimal and salivary gland function. In most patients, the primary syndrome runs a slow and benign course. The initial manifestations can be mucosal or nonspecific dryness, and 8–10 years may elapse from the initial symptoms to full-blown development of the disease.

The principal oral symptom of Sjögren's syndrome is dryness (xerostomia). Patients complain of difficulty in swallowing dry food, inability to speak continuously, a burning sensation, increase in dental caries, and problems in wearing complete dentures. Physical examination shows a dry, erythematous, sticky oral mucosa. There is atrophy of the filiform papillae on the dorsum of the tongue, and saliva from the major glands is either not expressible or cloudy. Enlargement of the parotid or other major salivary glands occurs in two-thirds of patients with primary Sjögren's syndrome, but is uncommon in those with the secondary syndrome. Diagnostic tests include sialometry, sialography, and scintigraphy. Newer imaging techniques including ultrasound, MRI or MR sialography of the major salivary glands are also being used. The labial minor salivary gland biopsy permits histopathologic confirmation of the focal lymphocytic infiltrates.

Ocular involvement is the other major manifestation of Sjögren's syndrome. Patients usually complain of a sandy or gritty feeling under the eyelids. Other symptoms include burning, accumulation of thick strands at the inner canthi, decreased tearing, redness, itching, eye fatigue, and increased photosensitivity. These symptoms are attributed to the destruction of corneal and bulbar conjunctival epithelium, defined as *keratoconjunctivitis sicca*. Diagnostic evaluation of keratoconjunctivitis sicca includes measurement of tear flow by Schirmer's I test and tear composition as assessed by the tear breakup time or tear lysozyme content. Slit-lamp examination of the cornea and conjunctiva after rose Bengal staining reveals punctuate corneal ulcerations and attached filaments of corneal epithelium.

Involvement of other exocrine glands occurs less frequently and includes a decrease in mucous gland secretions of the upper and lower respiratory tree, resulting in dry nose, throat, and trachea (xerotrachea), and diminished secretion of the exocrine glands of the gastrointestinal tract, leading to esophageal mucosal atrophy, atrophic gastritis, and subclinical pancreatitis. Dyspareunia due to dryness of the external genitalia and dry skin also may occur.

Extraglandular (systemic) manifestations are seen in one-third of patients with Sjögren's syndrome **(Table 9-2)**, while they are very rare in patients with Sjögren's syndrome associated with rheumatoid arthritis. These patients complain more often of easy fatigability, low-grade fever, Raynaud's phenomenon, myalgias, and arthralgias.

TABLE 9-2

PREVALENCE OF EXTRAGLANDULAR MANIFESTATIONS IN PRIMARY SJÖGREN'S SYNDROME

CLINICAL MANIFESTATION	PERCENT
Arthralgias/arthritis	60
Raynaud's phenomenon	37
Lymphadenopathy	14
Lung involvement	14
Vasculitis	11
Kidney involvement	9
Liver involvement	6
Lymphoma	6
Splenomegaly	3
Peripheral neuropathy	2
Myositis	1

Most patients with primary Sjögren's syndrome experience at least one episode of nonerosive arthritis during the course of their disease. Manifestations of pulmonary involvement are frequently evident histologically but rarely clinically important. Dry cough is the major manifestation that is attributed to small airway disease. Renal involvement includes interstitial nephritis, clinically manifested by hyposthenuria and renal tubular dysfunction with or without acidosis. Untreated acidosis may lead to nephrocalcinosis. Glomerulonephritis is a rare finding that occurs in patients with mixed cryoglobulinemia, or systemic lupus erythematosus overlapping with Sjögren's syndrome. Vasculitis affects small and medium-sized vessels. The most common clinical features are purpura, recurrent urticaria, skin ulcerations, glomerulonephritis, and mononeuritis multiplex. Sensorineural hearing loss was found in one-half of patients with Sjögren's syndrome and correlated with the presence of anticardiolipin antibodies.

It has been suggested that primary Sjögren's syndrome with vasculitis may also present with multifocal, recurrent, and progressive nervous system disease, such as hemiparesis, transverse myelopathy, hemisensory deficits, seizures, and movement disorders. Aseptic meningitis and multiple sclerosis also have been reported in these patients.

Lymphoma is a well-known manifestation of Sjögren's syndrome that usually presents later in the illness. Persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, and low C4 complement levels are manifestations suggesting the development of lymphoma. Interestingly, the same risk factors account for glomerulonephritis and lymphoma and are those that confer increased mortality. Most lymphomas are extranodal, low-grade marginal zone B cell lymphomas and are usually detected incidentally upon evaluating the labial biopsy. The affected lymph nodes are usually peripheral. Survival is decreased in patients with B symptoms, lymph node mass >7 cm in diameter, and high or intermediate histologic grade.

Routine laboratory tests reveal mild normochromic, normocytic anemia. An elevated erythrocyte sedimentation rate is found in approximately 70% of patients.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of primary Sjögren's syndrome is obtained if the patient presents with eye and/or mouth dryness, the eye tests disclose keratoconjunctivitis sicca, the mouth evaluation reveals the classic manifestations of the syndrome, and the patient's serum reacts with Ro/SS-A and/or La/SS-B autoantigens. Labial biopsy is needed when the diagnosis is uncertain or to rule out other conditions that may cause dry mouth or eyes or parotid gland enlargement **(Tables 9-3, 9-4)**. Validated diagnostic criteria have been established by a European study and have now been further improved by a European-American study group **(Table 9-5)**. Hepatitis C virus infection should be ruled out since, apart from serologic tests, the remainder of the clinicopathologic picture is almost identical to that of Sjögren's syndrome.

TABLE 9-3
DIFFERENTIAL DIAGNOSIS OF SICCA SYMPTOMS

XEROSTOMIA	DRY EYE	BILATERAL PAROTID GLAND ENLARGEMENT
Viral infections	Inflammation	Viral infections
Drugs	Stevens-Johnson syndrome	Mumps
Psychotherapeutic	Pemphigoid	Influenza
Parasympatholytic	Chronic conjunctivitis	Epstein-Barr
Antihypertensive	Chronic blepharitis	Coxsackievirus A
Psychogenic	Sjögren's syndrome	Cytomegalovirus
Irradiation	Toxicity	HIV
Diabetes mellitus	Burns	Sarcoidosis
Trauma	Drugs	Amyloidosis
Sjögren's syndrome	Neurologic conditions	Sjögren's syndrome
	Impaired lacrimal gland function	Metabolic
	Impaired eyelid function	Diabetes mellitus
	Miscellaneous	Hyperlipoproteinemias
	Trauma	Chronic pancreatitis
	Hypovitaminosis A	Hepatic cirrhosis
	Blink abnormality	Endocrine
	Anesthetic cornea	Acromegaly
	Lid scarring	Gonadal hypofunction
	Epithelial irregularity	

TABLE 9-4

DIFFERENTIAL DIAGNOSIS OF SJÖGREN'S SYNDROME

HIV INFECTION AND SICCA SYNDROME	SJÖGREN'S SYNDROME	SARCOIDOSIS
Predominant in young males	Predominant in middle-aged women	Invariable
Lack of autoantibodies to Ro/SS-A and/or La/SS-B	Presence of autoantibodies	Lack of autoantibodies to Ro/SS-A and/or La/SS-B
Lymphoid infiltrates of salivary glands by CD8+ lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and -DRw52	Unknown
Positive serologic tests for HIV	Negative serologic tests for HIV	Negative serologic tests for HIV

TABLE 9-5

REVISED INTERNATIONAL CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME[a,b,c]

I. Ocular symptoms: a positive response to at least one of three validated questions.
 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
 2. Do you have a recurrent sensation of sand or gravel in the eyes?
 3. Do you use tear substitutes more than three times a day?

II. Oral symptoms: a positive response to at least one of three validated questions.
 1. Have you had a daily feeling of dry mouth for more than 3 months?
 2. Have you had recurrent or persistently swollen salivary glands as an adult?
 3. Do you frequently drink liquids to aid in swallowing dry foods?

III. Ocular signs: objective evidence of ocular involvement defined as a positive result to at least one of the following two tests:
 1. Shirmer's I test, performed without anesthesia (≤5 mm in 5 min)
 2. Rose Bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands focal lymphocytic sialoadenitis, with a focus score ≥1.

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result to at least one of the following diagnostic tests:
 1. Unstimulated whole salivary flow (≤1.5 mL in 15 min)
 2. Parotid sialography
 3. Salivary scintigraphy

VI. Antibodies in the serum to Ro/SS-A or La/SS-B antigens, or both.

[a]Exclusion criteria: Past head and neck radiation treatment, hepatitis C infection, AIDS, preexisting lymphoma, sarcoidosis, graft-versus-host disease, use of anticholinergic drugs.
[b]Primary Sjögren's syndrome: any four of the six items, as long as item IV (histopathology) or VI (serology) is positive, or any three of the four objective criteria items (items III, IV, V, VI).
[c]In patients with a potentially associated disease (e.g., another well-defined connective tissue disease), the presence of item I or item II plus any two from among items III, IV, and V may be considered as indicative of secondary Sjögren's syndrome.
Source: From C Vitali et al: Ann Rheum Dis 61: 554, 2002. Copyright 2002 with permission from BMJ Publishing Group Ltd.

TREATMENT Sjögren's Syndrome

Treatment of Sjögren's syndrome is aimed at symptomatic relief and limiting the damaging local effects of chronic xerostomia and keratoconjunctivitis sicca by substituting or simulating the missing secretions (Fig. 9-1).

To replace deficient tears, there are several readily available ophthalmic preparations (Tearisol; Liquifilm; 0.5% methylcellulose; Hypo Tears). If corneal ulcerations are present, eye patching and boric acid ointments are recommended. Certain drugs that may decrease lacrimal and salivary secretion such as diuretics, antihypertensive drugs, anticholinergics, and antidepressants should be avoided.

For xerostomia the best replacement is water. Propionic acid gels may be used to treat vaginal dryness. To stimulate secretions, pilocarpine (5 mg thrice daily) or cevimeline (30 mg thrice daily) administered orally appears to improve sicca manifestations, and both are well tolerated. Hydroxychloroquine (200 mg) is helpful for arthralgias.

Patients with renal tubular acidosis should receive sodium bicarbonate orally (0.5–2 mmol/kg in four divided doses). Glucocorticoids (1 mg/kg per day) and/or immunosuppressive agents (e.g., cyclophosphamide) are indicated only for the treatment of systemic vasculitis. Anti–tumor necrosis factor agents are ineffective. Anti-CD20 monoclonal antibody therapy appears to be effective in patients with systemic disease and particularly with vasculitis, arthritis and fatigability. Combination of anti CD-20 with a classic CHOP regimen leads to increased survival in patients with high-grade lymphomas.

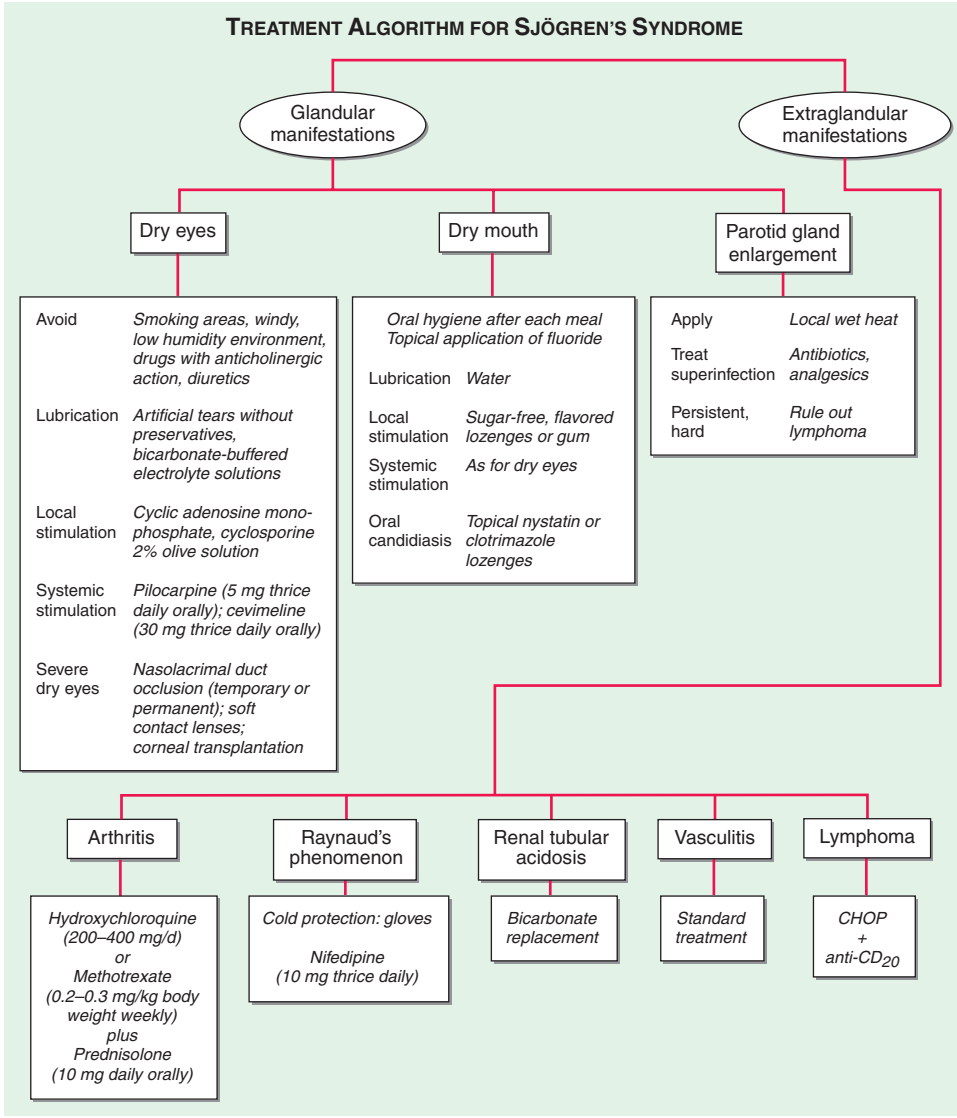


FIGURE 9-1
Treatment algorithm for Sjögren's syndrome.

CHAPTER 10

THE SPONDYLOARTHRITIDES

Joel D. Taurog

The spondyloarthritides are a group of overlapping disorders that share certain clinical features and genetic associations. These disorders include ankylosing spondylitis, reactive arthritis, psoriatic arthritis and spondylitis, enteropathic arthritis and spondylitis, juvenile-onset spondyloarthritis (SpA), and undifferentiated SpA. The similarities in clinical manifestations and genetic predisposition suggest that these disorders share pathogenic mechanisms.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory disorder of unknown cause that primarily affects the axial skeleton; peripheral joints and extraarticular structures are also frequently involved. The disease usually begins in the second or third decade; male to female prevalence is between 2:1 and 3:1. The term *axial spondyloarthritis*, coming into common use, includes early or mild forms that do not meet classical criteria for AS.

EPIDEMIOLOGY

AS shows a striking correlation with the histocompatibility antigen HLA-B27 and occurs worldwide roughly in proportion to the prevalence of B27 (Chap. 2). In North American whites, the prevalence of B27 is 7%, whereas it is 90% in patients with AS, independent of disease severity.

In population surveys, AS is present in 1–6% of adults inheriting B27, whereas the prevalence is 10–30% among B27+ adult first-degree relatives of AS probands. Concordance rate in identical twins is about 65%. Susceptibility to AS is determined largely by genetic factors, with B27 comprising up to one-half of the genetic component. Other HLA-linked genes may also contribute to susceptibility to AS. Genome-wide single-nucleotide polymorphism (SNP) analysis has identified additional susceptibility alleles in the genes encoding ERAP1 (chromosome 5q15) and IL-23R (chromosome 1p31.3). The genes encoding TNFSF15, TNFSF1A, STAT3, ANTXR2, and IL1R2, and at least six other chromosomal regions have also been implicated.

PATHOLOGY

The sites of axial inflammation in AS are inaccessible to routine biopsy and are rarely approached surgically. Knowledge of the axial histopathology is therefore based mostly on advanced cases. Sacroiliitis is often the earliest manifestations of AS. Synovitis, pannus, myxoid marrow, subchondral granulation tissue and marrow edema, enthesitis, and chondroid differentiation are found. Macrophages, T cells, and osteoclasts are prevalent. Eventually the eroded joint margins are gradually replaced by fibrocartilage regeneration and then by ossification. The joint may become totally obliterated.

In the spine, there is inflammatory granulation tissue at the junction of annulus fibrosis and vertebral bone. The outer annular fibers are eroded and eventually replaced by bone, forming the beginning of a syndesmophyte, which then grows by continued endochondral ossification, ultimately bridging the adjacent vertebral bodies. Ascending progression of this process leads to the "bamboo spine." Other lesions in the spine include diffuse osteoporosis, erosion of vertebral bodies at the disk margin, "squaring" or "barreling" of vertebrae, and inflammation and destruction of the disk-bone border. Inflammatory arthritis of the apophyseal joints is common, with erosion of cartilage by pannus, often followed by bony ankylosis. Bone mineral density is diminished in the spine and proximal femur early in the course of the disease.

Peripheral synovitis in AS shows marked vascularity, lining layer hyperplasia, lymphoid infiltration, and pannus formation. Central cartilaginous erosions caused by proliferation of subchondral granulation tissue are common.

Inflammation in the fibrocartilaginous enthesis, the region where a tendon, ligament, or joint capsule attaches to bone, is a characteristic lesion in AS and other SpA, both at axial and peripheral sites. Enthesitis is associated with prominent edema of the adjacent bone marrow and is often characterized by erosive lesions that eventually undergo ossification.

PATHOGENESIS

The pathogenesis of AS is thought to be immune-mediated, but there is no direct evidence for autoimmunity. There is uncertainty regarding the primary site of disease initiation. A unifying concept is that the AS disease process begins at sites where articular cartilage, ligaments, and other structures attach to bone. The dramatic response of the disease to therapeutic blockade of tumor necrosis factor α (TNF-α) indicates that this cytokine plays a central role in the immunopathogenesis of AS. There is recent evidence that T_H17 T cells and their cytokines may also play an important role.

The inflamed sacroiliac joint is infiltrated with CD4+ and CD8+ T cells and macrophages and shows high levels of TNF-α, particularly early in the disease. Abundant transforming growth factor β (TGF-β) has been found in more advanced lesions. Peripheral synovitis in AS and the other spondyloarthritides is characterized by neutrophils, macrophages expressing CD68 and CD163, CD4+ and CD8+ T cells, and B cells. There is prominent staining for intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), matrix metalloproteinase 3 (MMP-3), and myeloid-related proteins 8 and 14 (MRP-8 and MRP-14). Unlike rheumatoid arthritis (RA) synovium, citrullinated proteins and cartilage gp39 peptide–major histocompatibility complexes (MHCs) are absent. No specific event or exogenous agent that triggers the onset of disease has been identified, although overlapping features with reactive arthritis and inflammatory bowel disease (IBD) suggest that enteric bacteria may play a role. Triggering of innate immunity by microdamage at entheseal sites has recently been emphasized. Strong evidence that B27 plays a direct role is provided by genetic epidemiology studies and by the finding that rats transgenic for B27 spontaneously develop dramatic arthritis and spondylitis. However, the role of B27 remains unresolved. Since B27 rats lacking CD8+ T cells still develop arthritis and spondylitis, classical peptide antigen presentation to CD8+ T cells is probably not the primary disease mechanism. However, the association of AS with ERAP1, which strongly influences the MHC class I peptide repertoire, is only found in B27+ patients and suggests that peptide binding to B27 is nonetheless important. The B27 heavy chain has an unusual tendency to misfold, a process that may be proinflammatory. Genetic and functional studies in humans have suggested a role for natural killer (NK) cells in AS, possibly through interaction with B27. Defective dendritic cell function is a consistent feature of SpA-prone B27 rats not yet well investigated in patients.

CLINICAL MANIFESTATIONS

The symptoms of the disease are usually first noticed in late adolescence or early adulthood; the median age in Western countries is 23. In 5% of patients, symptoms begin after age 40. The initial symptom is usually dull pain, insidious in onset, felt deep in the lower lumbar or gluteal region, accompanied by low-back morning stiffness of up to a few hours' duration that improves with activity and returns following inactivity. Within a few months, the pain has usually become persistent and bilateral. Nocturnal exacerbation of pain often forces the patient to rise and move around.

In some patients, bony tenderness (presumably reflecting enthesitis or osteitis) may accompany back pain or stiffness, while in others it may be the predominant complaint. Common sites include the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels. Arthritis in the hips and shoulders ("root" joints) occurs in 25–35% of patients. Severe isolated hip arthritis or bony chest pain may be the presenting complaint. Arthritis of peripheral joints other than the hips and shoulders, usually asymmetric, occurs in up to 30% of patients. Neck pain and stiffness from involvement of the cervical spine are usually relatively late manifestations but are occasionally dominant symptoms. Rare patients, particularly in the older age group, present with predominantly constitutional symptoms.

AS often has a juvenile onset in developing countries. Peripheral arthritis and enthesitis usually predominate, with axial symptoms supervening in late adolescence.

Initially, physical findings mirror the inflammatory process. The most specific findings involve loss of spinal mobility, with limitation of anterior and lateral flexion and extension of the lumbar spine and of chest expansion. Limitation of motion is usually out of proportion to the degree of bony ankylosis, reflecting muscle spasm secondary to pain and inflammation. Pain in the sacroiliac joints may be elicited either with direct pressure or with stress on the joints. In addition, there is commonly tenderness upon palpation at the sites of symptomatic bony tenderness and paraspinous muscle spasm.

The modified Schober test is a useful measure of lumbar spine flexion. The patient stands erect, with heels together, and marks are made on the spine at the lumbosacral junction (identified by a horizontal line between the posterosuperior iliac spines) and 10 cm above. The patient then bends forward maximally with

knees fully extended, and the distance between the two marks is measured. This distance increases by ≥5 cm in the case of normal mobility and by <4 cm in the case of decreased mobility. Chest expansion is measured as the difference between maximal inspiration and maximal forced expiration in the fourth intercostal space in males or just below the breasts in females, with the patient's hands resting on or just behind the head. Normal chest expansion is ≥5 cm.

Limitation or pain with motion of the hips or shoulders is usually present if these joints are involved. It should be emphasized that early in the course of mild cases, symptoms may be subtle and nonspecific, and the physical examination may be completely normal.

The course of the disease is extremely variable, ranging from the individual with mild stiffness and normal radiographs to the patient with a totally fused spine and severe bilateral hip arthritis, accompanied by severe peripheral arthritis and extraarticular manifestations. Pain tends to be persistent early in the disease and then becomes intermittent, with alternating exacerbations and quiescent periods. In a typical severe untreated case with progression of the spondylitis to syndesmophyte formation, the patient's posture undergoes characteristic changes, with obliterated lumbar lordosis, buttock atrophy, and accentuated thoracic kyphosis. There may be a forward stoop of the neck or flexion contractures at the hips, compensated by flexion at the knees. Disease progression can be estimated clinically from loss of height, limitation of chest expansion and spinal flexion, and occiput-to-wall distance. Occasional individuals are encountered with advanced deformities who report having never had significant symptoms.

There is little consensus regarding the factors that predict disease progression and functional outcome. In some but not all studies, onset of AS in adolescence and early hip involvement correlate with a worse prognosis. AS in women tends to progress less frequently to total spinal ankylosis, although there is some evidence for an increased prevalence of isolated cervical ankylosis and peripheral arthritis in women. In industrialized countries, peripheral arthritis (distal to hips and shoulders) occurs in less than one-half of patients with AS, usually as a late manifestation, whereas in developing countries, the prevalence is much higher, with onset typically early in the disease course. Pregnancy has no consistent effect on AS, with symptoms improving, remaining the same, or deteriorating in about one-third of pregnant patients, respectively. Smoking correlates with adverse outcome.

The most serious complication of the spinal disease is spinal fracture, which can occur with even minor trauma to the rigid, osteoporotic spine. The lower cervical spine is most commonly involved. These fractures are often displaced and cause spinal cord injury. A recent survey suggested a >10% lifetime risk of fracture. Occasionally, fracture through a diskovertebral junction and adjacent neural arch, termed *pseudoarthrosis*, most common in the thoracolumbar spine, can be an unrecognized source of persistent localized pain and/or neurologic dysfunction. Wedging of thoracic vertebrae is common and correlates with accentuated kyphosis.

The most common extraarticular manifestation is acute anterior uveitis, which occurs in 40% of patients and can antedate the spondylitis. Attacks are typically unilateral, causing pain, photophobia, and increased lacrimation. These tend to recur, often in the opposite eye. Cataracts and secondary glaucoma are not uncommon sequelae. Up to 60% of patients have inflammation in the colon or ileum. This is usually asymptomatic, but frank IBD occurs in 5–10% of patients with AS (see "Enteropathic Arthritis," later in the chapter). About 10% of patients meeting criteria for AS have psoriasis (see "Psoriatic Arthritis," later in the chapter). Aortic insufficiency, sometimes leading to congestive heart failure, occurs in a few percent of patients, occasionally early in the course of the spinal disease but usually after prolonged disease. Third-degree heart block may occur alone or together with aortic insufficiency. Subclinical pulmonary lesions and cardiac dysfunction may be relatively common. Cauda equina syndrome and upper pulmonary lobe fibrosis are rare late complications. Retroperitoneal fibrosis is a rare associated condition. Prostatitis has been reported to have an increased prevalence. Amyloidosis is rare (Chap. 16).

Several validated measures of disease activity and functional outcome are in widespread use in the study and management of AS, particularly the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a measure of disease activity; the Bath Ankylosing Spondylitis Functional Index (BASFI), a measure of limitation in activities of daily living; and several measures of radiographic changes. Despite persistence of the disease, most patients remain gainfully employed. Some but not all studies of survival in AS have suggested that AS shortens life span, compared with the general population. Mortality attributable to AS is largely the result of spinal trauma, aortic insufficiency, respiratory failure, amyloid nephropathy, or complications of therapy such as upper gastrointestinal hemorrhage. The impact of anti-TNF therapy on outcome and mortality is not yet known, but there is evidence for significantly improved work productivity.

LABORATORY FINDINGS

No laboratory test is diagnostic of AS. In most ethnic groups, HLA-B27 is present in 80–90% of patients. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often, but not always, elevated. Mild anemia may be present. Patients with severe disease may show an elevated alkaline phosphatase level. Elevated serum IgA levels are common. Rheumatoid factor, anti-cyclic

citrullinated peptide (CCP), and antinuclear antibodies (ANAs) are largely absent unless caused by a coexistent disease, although ANAs may appear with anti-TNF therapy. Synovial fluid from peripheral joints in AS is nonspecifically inflammatory. In cases with restriction of chest wall motion, decreased vital capacity and increased functional residual capacity are common, but airflow is normal and ventilatory function is usually well maintained.

RADIOGRAPHIC FINDINGS

Radiographically demonstrable sacroiliitis is eventually present in AS. The earliest changes by standard radiography are blurring of the cortical margins of the subchondral bone, followed by erosions and sclerosis. Progression of the erosions leads to "pseudowidening" of the joint space; as fibrous and then bony ankylosis supervene, the joints may become obliterated. The changes and progression of the lesions are usually symmetric.

In the lumbar spine, progression of the disease leads to straightening, caused by loss of lordosis, and reactive sclerosis, caused by osteitis of the anterior corners of the vertebral bodies with subsequent erosion, leading to "squaring" or even "barreling" of one or more vertebral bodies. Progressive ossification leads to eventual formation of marginal syndesmophytes, visible on plain films as bony bridges connecting successive vertebral bodies anteriorly and laterally.

In many cases, years may elapse before unequivocal sacroiliac abnormalities are evident on plain radiographs, and consequently magnetic resonance imaging (MRI) is being increasingly used in diagnosing AS. Active sacroiliitis is best visualized by dynamic MRI with fat saturation, either T2-weighed turbo spin-echo sequence or short tau inversion recovery (STIR) with high resolution, or T1-weighted images with contrast enhancement. These techniques are much more sensitive than conventional radiography for identifying early intraarticular inflammation, cartilage changes, and underlying bone marrow edema in sacroiliitis **(Fig. 10-1)**. They are also highly sensitive for evaluation of acute and chronic spinal changes **(Fig. 10-2)**.

Reduced bone mineral density can be detected by dual-energy x-ray absorptiometry of the femoral neck and the lumbar spine. By using a lateral projection of the L3 vertebral body, falsely elevated readings related to spinal ossification can be avoided.

DIAGNOSIS

It is important to establish the diagnosis of early AS before the development of irreversible deformity. This goal presents a challenge for several reasons: (1) Back pain is very common, but AS is much less common; (2) an early presumptive diagnosis often relies on clinical

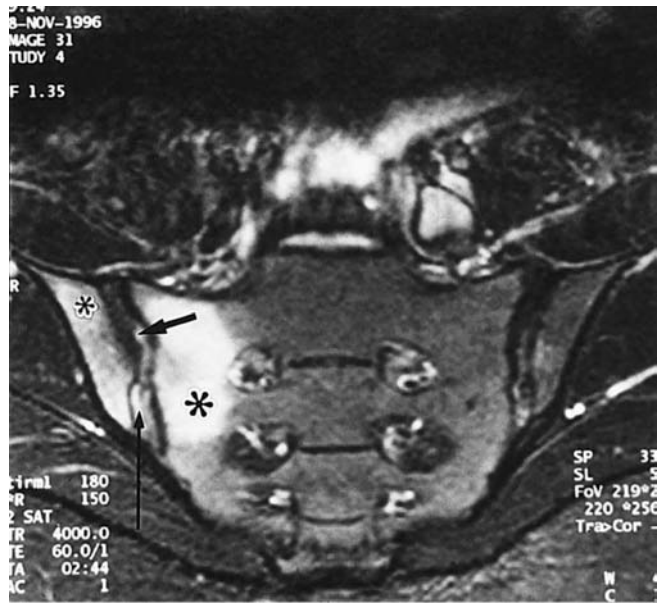


FIGURE 10-1
Early sacroiliitis in a patient with AS, indicated by prominent edema in the juxtaarticular bone marrow (asterisks), synovium and joint capsule (thin arrow), and interosseous ligaments (thick arrow) on a STIR (short tau inversion recovery) magnetic resonance image. (*From M Bollow et al: Zeitschrift für Rheumatologie 58:61, 1999. Reproduced with permission.*)

grounds requiring considerable expertise; and (3) young individuals with early AS are often reluctant to seek medical care. The widely used modified New York criteria (1984) are based on the presence of definite radiographic sacroiliitis and are too insensitive in early or mild cases. In 2009, new criteria for axial SpA were proposed by the Assessment of Spondylo Arthritis International Society (ASAS) **(Table 10-1)**. They are applicable to individuals with ≥3 months of back pain with age of onset <45 years old. Active inflammation of the sacroiliac (SI) joints as determined by dynamic MRI is considered equivalent to the older criterion of definite radiographic sacroiliitis (discussed later).

AS must be differentiated from numerous other causes of low-back pain, some far more common than AS. To qualify as the criterion for inflammatory back pain of axial SpA (Table 10-1), the chronic (≥3 months) back pain should have four or more of these characteristic features: (1) age of onset below 40 years old, (2) insidious onset, (3) improvement with exercise and (4) no improvement with rest, and (5) pain at night with improvement upon getting up. Other common features of inflammatory back pain include morning stiffness >30 min, awakening from back pain during only the second half of the night, and alternating buttock pain. In clinical decision-making, all of these features are additive. The most common causes of back pain other than AS are primarily mechanical or degenerative rather than

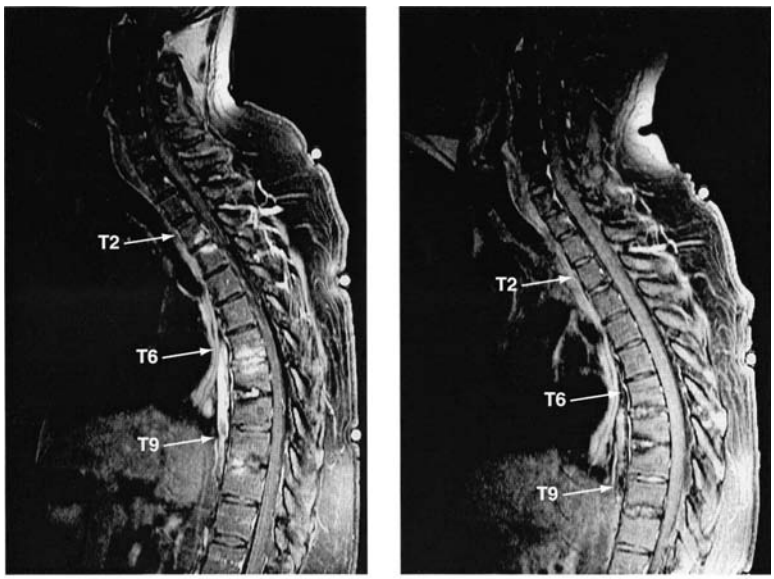


FIGURE 10-2
Spinal inflammation (spondylodiskitis) in a patient with AS and its dramatic response to treatment with infliximab. Gadolinium-enhanced T1-weighted magnetic resonance images, with fat saturation, at baseline and after 24 weeks of infliximab therapy. (*From J Braun et al: Ann Rheum Dis 67:340, 2009.*)

TABLE 10-1

ASAS CRITERIA FOR CLASSIFICATION OF AXIAL SPONDYLOARTHRITIS (TO BE APPLIED FOR PATIENTS WITH BACK PAIN ≥3 MONTHS AND AGE OF ONSET <45 YEARS)[a]

SACROILIITIS ON IMAGING OR PLUS ≥1 SpA FEATURE	HLA-B27 PLUS ≥2 OTHER SpA FEATURES
Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of SpA-associated sacroiliiti[b] and/or • Definite radiographic sacroiliitis according to modified New York criteria[c]	SpA features • Inflammatory back pain[d] • Arthritis[e] • Enthesitis (heel)[f] • Anterior uveitis[g] • Dactylitis[e] • Psoriasis[e] • Crohn's disease or ulcerative colitis[e] • Good response to NSAIDs[h] • Family history of SpA[i] • HLA-B27 • Elevated CRP[j]

[a]Sensitivity 83%, specificity 84%. The imaging arm (sacroiliitis) alone has a sensitivity of 66% and a specificity of 97%.
[b]Bone marrow edema and/or osteitis on short tau inversion recovery (STIR) or gadolinium-enhanced T1 image.
[c]Bilateral grade ≥2 or unilateral grade 3 or 4.
[d]See text for criteria.
[e]Past or present, diagnosed by a physician.
[f]Past or present pain or tenderness on examination at calcaneus insertion of Achilles tendon or plantar fascia.
[g]Past or present, confirmed by an ophthalmologist.
[h]Substantial relief of back pain at 24–48 h after a full dose of NSAID.
[i]First- or second-degree relatives with ankylosing spondylitis (AS), psoriasis, uveitis, reactive arthritis (ReA), or inflammatory bowel disease (IBD).
[j]After exclusion of other causes of elevated CRP.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CRP, C-reactive protein; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis.
Source: From M Rudwaleit et al: Ann Rheum Dis 68:777, 2009. Copyright 2009, with permission from BMJ Publishing Group Ltd.

primarily inflammatory and tend not to show clustering of these features.

Less-common metabolic, infectious, and malignant causes of back pain must also be differentiated from AS, including infectious spondylitis, spondylodiskitis, and sacroiliitis, and primary or metastatic tumor. Ochronosis can produce a phenotype that is clinically and radiographically similar to AS. Calcification and ossification of paraspinous ligaments occur in *diffuse idiopathic skeletal hyperostosis* (DISH), which occurs in the middle-aged and elderly and is usually not symptomatic. Ligamentous calcification gives the appearance of "flowing wax" on the anterior bodies of the vertebrae. Intervertebral disk spaces are preserved, and sacroiliac and apophyseal joints appear normal, helping to differentiate DISH from spondylosis and from AS, respectively.

TREATMENT Ankylosing Spondylitis

All management of AS should include an exercise program designed to maintain posture and range of motion. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of pharmacologic therapy for AS. These agents reduce pain and tenderness and increase mobility in many patients with AS. There is evidence that daily NSAID therapy slows radiographic progression. However, many patients with AS have continued symptoms and develop deformity despite NSAID therapy. Beginning in 2000, dramatic responses to anti-TNF-α therapy were reported in patients with AS and other spondyloarthritides. Patients with AS treated with either infliximab (chimeric human/mouse anti-TNF-α monoclonal antibody), etanercept (soluble p75 TNF-α receptor–IgG fusion protein), or adalimumab or golimumab (human anti-TNF-α monoclonal antibodies) have shown rapid,

profound, and sustained reductions in all clinical and laboratory measures of disease activity. Patients with long-standing disease and even some with complete spinal ankylosis have shown significant improvement in both objective and subjective indicators of disease activity and function, including morning stiffness, pain, spinal mobility, peripheral joint swelling, CRP, and ESR. MRI studies indicate substantial resolution of bone marrow edema, enthesitis, and joint effusions in the sacroiliac joints, spine, and peripheral joints (Fig. 10-2). Similar results have been obtained in large randomized controlled trials of all four agents and many open-label studies. About one-half of the patients achieve a ≥50% reduction in the BASDAI. The response tends to be stable over time, and partial or full remissions are common. Increased bone mineral density is found as early as 24 weeks after onset of therapy. There is evidence that anti-TNF therapy does not prevent syndesmophyte formation, although the practical clinical significance of this is not yet clear. A mechanism for this has been proposed based on the observation that TNF-α inhibits new bone formation by upregulating DKK-1, a negative regulator of the wingless (Wnt) signaling pathway that promotes osteoblast activity. Serum DKK-1 levels are inappropriately low in AS patients and are also suppressed by anti-TNF therapy.

The dosages of anti-TNF agents used in AS patients have usually been similar to those in RA. Infliximab is given intravenously, 3–5 mg/kg body weight, and then repeated 2 weeks later, again 6 weeks later, and then at 8-week intervals. Etanercept is given by subcutaneous injection, 50 mg once weekly. Adalimumab is given by subcutaneous injection, 40 mg biweekly. Golimumab is given by subcutaneous injection, 50 or 100 mg every 4 weeks.

Although these potent immunosuppressive agents have so far been relatively safe, seven types of side effects are not rare: (1) serious infections, including disseminated tuberculosis; (2) hematologic disorders, such as pancytopenia; (3) demyelinating disorders; (4) exacerbation of congestive heart failure; (5) systemic lupus erythematosus–related autoantibodies and clinical features; (6) hypersensitivity infusion or injection site reactions; and (7) severe liver disease. No increased incidence of malignancy has been observed in AS patients treated for over 5 years.

Because of the expense, potentially serious side effects, and unknown long-term effects of these agents, their use should be restricted to patients with a definite diagnosis and active disease (BASDAI ≥4 out of 10 and expert opinion) that is inadequately responsive to therapy with at least two different NSAIDs. Before initiation of anti-TNF therapy, all patients should be tested for tuberculin (TB) reactivity, and reactors (≥5 mm) should be treated with anti-TB agents. Contraindications include active infection or high risk of infection; malignancy or premalignancy; and history of systemic lupus erythematosus, multiple sclerosis, or related autoimmunity. Pregnancy and breast-feeding are relative contraindications. Continuation beyond 12 weeks of therapy requires either a 50% reduction in BASDAI or absolute reduction of ≥2 out of 10, and favorable expert opinion. Sulfasalazine, in doses of 2–3 g/d, has been shown to be of modest benefit, primarily for peripheral arthritis. A therapeutic trial of this agent should precede any use of anti-TNF agents in patients with predominantly peripheral arthritis. Methotrexate, although widely used, has not been shown to be of benefit in AS, nor has any therapeutic role for gold or oral glucocorticoids been documented. Potential benefit in AS has been reported for thalidomide, 200 mg/d, perhaps acting through inhibition of TNF-α.

The most common indication for surgery in patients with AS is severe hip joint arthritis, the pain and stiffness of which are usually dramatically relieved by total hip arthroplasty. Rare patients may benefit from surgical correction of extreme flexion deformities of the spine or of atlantoaxial subluxation.

Attacks of uveitis are usually managed effectively with local glucocorticoid administration in conjunction with mydriatic agents, although systemic glucocorticoids, immunosuppressive drugs, or anti-TNF therapy may be required. TNF inhibitors reduce the frequency of attacks of uveitis in patients with AS, although cases of new or recurrent uveitis after use of a TNF inhibitor have been observed, especially with etanercept.

Coexistent cardiac disease may require pacemaker implantation and/or aortic valve replacement. Management of axial osteoporosis is at present similar to that used for primary osteoporosis, since data specific for AS are not available.

REACTIVE ARTHRITIS

Reactive arthritis (ReA) refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. In recent years, the term has been used primarily to refer to SpA following enteric or urogenital infections.

Other forms of reactive and infection-related arthritis not associated with B27 and showing a spectrum of clinical features different from SpA include Lyme disease and rheumatic fever (Chap. 7).

HISTORIC BACKGROUND

The association of acute arthritis with episodes of diarrhea or urethritis has been recognized for centuries. A large number of cases during World Wars I and II

focused attention on the triad of arthritis, urethritis, and conjunctivitis, often with additional mucocutaneous lesions, which became widely known by eponyms that are now of historic interest only.

The identification of bacterial species capable of triggering the clinical syndrome and the finding that many patients possess the B27 antigen led to the unifying concept of ReA as a clinical syndrome triggered by specific etiologic agents in a genetically susceptible host. A similar spectrum of clinical manifestations can be triggered by enteric infection with any of several *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter* species; by genital infection with *Chlamydia trachomatis*; and by other agents as well. The triad of arthritis, urethritis, and conjunctivitis represents a small part of the spectrum of the clinical manifestations of ReA. For the purposes of this chapter, the use of the term *ReA* will be restricted to those cases of SpA in which there is at least presumptive evidence for a related antecedent infection. Patients with clinical features of ReA who lack evidence of an antecedent infection will be considered to have *undifferentiated spondyloarthritis*, discussed later.

EPIDEMIOLOGY

Following the first reports of association of ReA with HLA-B27, in most hospital-based series in which *Shigella*, *Yersinia*, or *Chlamydia* were the triggering infectious agents, 60–85% of patients were found to be B27-positive, with a lower prevalence in ReA triggered by *Salmonella* and *Campylobacter*. In more recent community-based or common-source epidemic studies, the prevalence of B27 in ReA has often been below 50%, and in some instances not elevated at all. The most common age range is 18–40 years, but ReA can occur in children over 5 years of age and in older adults.

The gender ratio in ReA following enteric infection is nearly 1:1, whereas venereally acquired ReA occurs mainly in men. The overall prevalence and incidence of ReA are difficult to assess because of the variable prevalence of triggering infections and genetic susceptibility factors in different populations. In Scandinavia, an annual incidence of 10–28:100,000 has been reported. The spondylo-arthritides were formerly almost unknown in sub-Saharan Africa. However, ReA and other peripheral SpA have now become the most common rheumatic diseases in Africans in the wake of the AIDS epidemic, without association to B27, which is very rare in these populations. SpA in Africans with HIV infection usually occurs in individuals with stage I disease (as classified by the World Health Organization). It is often the first manifestation of infection and often remits with disease progression. In contrast, Western white patients with HIV and SpA are usually B27-positive, and the arthritis flares as AIDS advances.

PATHOLOGY

Synovial histology is similar to that of other SpA. Enthesitis shows increased vascularity and macrophage infiltration of fibrocartilage. Microscopic histopathologic evidence of inflammation has occasionally been noted in the colon and ileum of patients with post-venereal ReA, but much less commonly than in postenteric ReA. The skin lesions of keratoderma blenorrhagica, associated mainly with venereally acquired ReA, are histologically indistinguishable from psoriatic lesions.

ETIOLOGY AND PATHOGENESIS

Of the four *Shigella* species *S. sonnei*, *S. boydii*, *S. flexneri*, and *S. dysenteriae*, *S. flexneri* has most often been implicated in cases of ReA, both sporadic and epidemic. *S. sonnei* and *S. dysenteriae* trigger some cases of ReA.

Other bacteria identified definitively as triggers of ReA include several *Salmonella* spp., *Yersinia enterocolitica*, *Y. pseudotuberculosis, Campylobacter jejuni*, and *Chlamydia trachomatis*. There is also evidence implicating *Clostridium difficile*, *Campylobacter coli*, certain toxigenic *E. coli*, and possibly *Ureaplasma urealyticum* and *Mycoplasma genitalium*. Respiratory infection with *Chlamydia pneumoniae* has also been implicated. There are also numerous isolated reports of acute arthritis preceded by other bacterial, viral, or parasitic infections, and even following intravesicular bacillus Calmette-Guérin (BCG) treatment for bladder cancer.

It has not been determined whether ReA occurs by the same pathogenic mechanism following infection with each of these microorganisms, nor has the mechanism been elucidated in the case of any one of the known bacterial triggers. Most, if not all, of the organisms well established to be triggers produce lipopolysaccharide (LPS) and share a capacity to attack mucosal surfaces, to invade host cells, and to survive intracellularly. Antigens from *Chlamydia*, *Yersinia*, *Salmonella*, and *Shigella* have been shown to be present in the synovium and/or synovial fluid leukocytes of patients with ReA for long periods following the acute attack. In ReA triggered by *Y. enterocolitica*, bacterial LPS and heat-shock protein antigens have been found in peripheral blood cells years after the triggering infection. *Yersinia* DNA and *C. trachomatis* DNA and RNA have been detected in synovial tissue from ReA patients, suggesting the presence of viable organisms despite uniform failure to culture the organism from these specimens. The specificity of these findings is unclear, however, since chromosomal bacterial DNA has also been found in synovium in other rheumatic diseases, and 16S rRNA from a very wide variety of bacteria has been found in ReA synovium. In several older studies, synovial T cells that specifically responded to antigens of the inciting organism were reported and characterized

as predominantly CD4+ with a T_H2 or T regulatory phenotype. More recent work has documented high levels of IL-17 in ReA synovial fluid, but the source has not been identified. HLA-B27 seems to be associated with more severe and chronic forms of ReA, but its pathogenic role remains to be determined. HLA-B27 significantly prolongs the intracellular survival of *Y. enterocolitica* and *S. enteritidis* in human and mouse cell lines. Prolonged intracellular bacterial survival, promoted by B27, other factors, or both, may permit trafficking of infected leukocytes from the site of primary infection to joints, where an innate and/or adaptive immune response to persistent bacterial antigens may then promote arthritis.

CLINICAL FEATURES

The clinical manifestations of ReA constitute a spectrum that ranges from an isolated, transient monarthritis or enthesitis to severe multisystem disease. A careful history will usually elicit evidence of an antecedent infection 1–4 weeks before onset of symptoms of the reactive disease. However, in a sizable minority, no clinical or laboratory evidence of an antecedent infection can be found. In cases of presumed venereally acquired reactive disease, there is often a history of a recent new sexual partner, even without laboratory evidence of infection.

Constitutional symptoms are common, including fatigue, malaise, fever, and weight loss. The musculoskeletal symptoms are usually acute in onset. Arthritis is usually asymmetric and additive, with involvement of new joints occurring over a few days to 1–2 weeks. The joints of the lower extremities, especially the knee, ankle, and subtalar, metatarsophalangeal, and toe interphalangeal joints, are most commonly involved, but the wrist and fingers can be involved as well. The arthritis is usually quite painful, and tense joint effusions are not uncommon, especially in the knee. Patients often cannot walk without support. Dactylitis, or "sausage digit," a diffuse swelling of a solitary finger or toe, is a distinctive feature of ReA and other peripheral spondyloarthritides but can be seen in polyarticular gout and sarcoidosis. Tendinitis and fasciitis are particularly characteristic lesions, producing pain at multiple insertion sites (entheses), especially the Achilles insertion, the plantar fascia, and sites along the axial skeleton. Spinal and low-back pain are quite common and may be caused by insertional inflammation, muscle spasm, acute sacroiliitis, or, presumably, arthritis in intervertebral joints.

Urogenital lesions may occur throughout the course of the disease. In males, urethritis may be marked or relatively asymptomatic and may be either an accompaniment of the triggering infection or a result of the reactive phase of the disease. Prostatitis is also common. Similarly, in females, cervicitis or salpingitis may be caused either by the infectious trigger or by the sterile reactive process.

Ocular disease is common, ranging from transient, asymptomatic conjunctivitis to an aggressive anterior uveitis that occasionally proves refractory to treatment and may result in blindness.

Mucocutaneous lesions are frequent. Oral ulcers tend to be superficial, transient, and often asymptomatic. The characteristic skin lesions, *keratoderma blenorrhagica*, consist of vesicles that become hyperkeratotic, ultimately forming a crust before disappearing. They are most common on the palms and soles but may occur elsewhere as well. In patients with HIV infection, these lesions are often extremely severe and extensive, sometimes dominating the clinical picture. Lesions may occur on the glans penis, termed *circinate balanitis*; these consist of vesicles that quickly rupture to form painless superficial erosions, which in circumcised individuals can form crusts similar to those of keratoderma blenorrhagica. Nail changes are common and consist of onycholysis, distal yellowish discoloration, and/or heaped-up hyperkeratosis.

Less-frequent or rare manifestations of ReA include cardiac conduction defects, aortic insufficiency, central or peripheral nervous system lesions, and pleuropulmonary infiltrates.

Arthritis typically persists 3–5 months, but courses up to 1 year can occur. Chronic joint symptoms persist in about 15% of patients and in up to 60% in hospital-based series. Recurrences of the acute syndrome are also common. Work disability or forced change in occupation are common in those with persistent joint symptoms. Chronic heel pain is often particularly distressing. Low-back pain, sacroiliitis, and frank AS are also common sequelae. In most studies, HLA-B27–positive patients have shown a worse outcome than B27-negative patients. Patients with *Yersinia*- or *Salmonella*- induced arthritis have less chronic disease than those whose initial episode follows epidemic shigellosis.

LABORATORY AND RADIOGRAPHIC FINDINGS

The ESR and acute-phase reactants are usually elevated during the acute phase of the disease. Mild anemia may be present. Synovial fluid is nonspecifically inflammatory. In most ethnic groups, about one-half of the patients are B27-positive. The triggering infection usually does not persist at the site of primary mucosal infection through the time of onset of the reactive disease, but it may be possible to culture the organism, e.g., in the case of *Yersinia*- or *Chlamydia*-induced disease. Serologic evidence of a recent infection may be present, such as a marked elevation of antibodies to *Yersinia*,

Salmonella, or *Chlamydia*. Polymerase chain reaction (PCR) for chlamydial DNA in first-voided urine specimens is said to have high sensitivity.

In early or mild disease, radiographic changes may be absent or confined to juxtaarticular osteoporosis. With long-standing persistent disease, marginal erosions and loss of joint space can be seen in affected joints. Periostitis with reactive new bone formation is characteristic, as in all the SpA. Spurs at the insertion of the plantar fascia are common.

Sacroiliitis and spondylitis may be seen as late sequelae. Sacroiliitis is more commonly asymmetric than in AS, and spondylitis, rather than ascending symmetrically, can begin anywhere along the lumbar spine. The syndesmophytes may be asymmetric, coarse and nonmarginal, arising from the middle of a vertebral body, a pattern less commonly seen in primary AS. Progression to spinal fusion is uncommon.

DIAGNOSIS

ReA is a clinical diagnosis with no definitively diagnostic laboratory test or radiographic finding. The diagnosis should be entertained in any patient with an acute inflammatory, asymmetric, additive arthritis or tendinitis. The evaluation should include questioning regarding possible triggering events such as an episode of diarrhea or dysuria. On physical examination, attention must be paid to the distribution of the joint and tendon involvement and to possible sites of extraarticular involvement, such as the eyes, mucous membranes, skin, nails, and genitalia. Synovial fluid analysis may be helpful in excluding septic or crystal-induced arthritis. Culture, serology, or molecular methods may help to identify a triggering infection.

Although typing for B27 has low negative predictive value in ReA, it may have prognostic significance in terms of severity, chronicity, and the propensity for spondylitis and uveitis. Furthermore, if positive, it can be helpful diagnostically in atypical cases. HIV testing is often indicated and may be necessary in order to select appropriate therapy.

It is important to differentiate ReA from disseminated gonococcal disease, both of which can be venereally acquired and associated with urethritis. Unlike ReA, gonococcal arthritis and tenosynovitis tend to involve both upper and lower extremities equally, to lack back symptoms, and to be associated with characteristic vesicular skin lesions. A positive gonococcal culture from the urethra or cervix does not exclude a diagnosis of ReA; however, culturing gonococci from blood, skin lesion, or synovium establishes the diagnosis of disseminated gonococcal disease. PCR assay for *N. gonorrhoeae* and *C. trachomatis* may be helpful. Occasionally, only a therapeutic trial of antibiotics can distinguish the two.

ReA shares many features in common with psoriatic arthropathy. However, psoriatic arthritis is usually gradual in onset; the arthritis tends to affect primarily the upper extremities; there is less associated periarthritis; and there are usually no associated mouth ulcers, urethritis, or bowel symptoms.

TREATMENT Reactive Arthritis

Most patients with ReA benefit to some degree from high-dose NSAIDs, although acute symptoms are rarely completely ameliorated, and some patients fail to respond at all. Indomethacin, 75–150 mg/d in divided doses, is the initial treatment of choice, but other NSAIDs may be tried.

Prompt, appropriate antibiotic treatment of acute chlamydial urethritis or enteric infection may prevent the emergence of ReA. However, several controlled trials have failed to demonstrate any benefit for antibiotic therapy that is initiated after onset of arthritis. One long-term follow-up study suggested that although antibiotic therapy had no effect on the acute episode of ReA, it helped prevent subsequent chronic SpA. Another such study failed to demonstrate any long-term benefit. A promising recent double-blind placebo-controlled study showed that a majority of patients with chronic ReA due to *Chlamydia* benefited significantly from a 6-month course of rifampin 300 mg daily plus azithromycin 500 mg daily for 5 days then twice weekly, or 6 months of rifampin 300 mg daily plus doxycycline 100 mg twice daily.

Multicenter trials have suggested that sulfasalazine, up to 3 g/d in divided doses, may be beneficial to patients with persistent ReA.[1] Patients with persistent disease may respond to azathioprine, 1–2 mg/kg per day, or to methotrexate, up to 20 mg per week. Although no controlled trials of anti-TNF-α in ReA have been reported, anecdotal evidence supports the use of these agents in severe chronic cases, although lack of response has also been observed.[1]

Tendinitis and other enthesitic lesions may benefit from intralesional glucocorticoids. Uveitis may require aggressive treatment to prevent serious sequelae (discussed earlier). Skin lesions ordinarily require only symptomatic treatment. In patients with HIV infection and ReA, many of whom have severe skin lesions, the skin lesions in particular respond to antiretroviral therapy. Cardiac complications are managed conventionally; management of neurologic complications is symptomatic.

[1]Azathioprine, methotrexate, sulfasalazine, pamidronate, and thalidomide have not been approved for this purpose by the U.S. Food and Drug Administration at the time of publication.

Comprehensive management includes counseling of patients in the avoidance of sexually transmitted disease and exposure to enteropathogens, as well as appropriate use of physical therapy, vocational counseling, and continued surveillance for long-term complications such as ankylosing spondylitis.

PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) refers to an inflammatory arthritis that characteristically occurs in individuals with psoriasis.

HISTORIC BACKGROUND

The association between arthritis and psoriasis was noted in the nineteenth century. In the 1960s, on the basis of epidemiologic and clinical studies, it became clear that unlike RA the arthritis associated with psoriasis was usually seronegative, often involved the distal interphalangeal (DIP) joints of the fingers and the spine and sacroiliac joints, had distinctive radiographic features, and showed considerable familial aggregation. In the 1970s, PsA was included in the broader category of the spondyloarthritides because of features similar to those of AS and ReA.

EPIDEMIOLOGY

Estimates of the prevalence of PsA among individuals with psoriasis range from 5% to 30%. In white populations, psoriasis is estimated to have a prevalence of 1–3%. Psoriasis and PsA are less common in other races in the absence of HIV infection, and the prevalence of PsA in individuals with psoriasis may be less common. First-degree relatives of PsA patients have an elevated risk for psoriasis, for PsA itself, and for other forms of SpA. Of patients with psoriasis, up to 30% have an affected first-degree relative. In monozygotic twins, the reported concordance for psoriasis varies from 35% to 72%, and for PsA from 10% to 30%. A variety of HLA associations have been found. The HLA-Cw6 gene is directly associated with psoriasis, particularly familial juvenile-onset (type I) psoriasis. HLA-B27 is associated with psoriatic spondylitis (discussed later). HLA-DR7, -DQ3, and -B57 are associated with PsA because of linkage disequilibrium with Cw6. Other associations with PsA include HLA-B13, -B37, -B38, -B39, and DR4. A recent genome-wide scan found association of both psoriasis and PsA with a polymorphism at the HCP5 locus closely linked to HLA-B, and also to IL-23R, IL-12B (chromosome 5q31), and several other chromosomal regions.

PATHOLOGY

The inflamed synovium in PsA resembles that of RA, although with somewhat less hyperplasia and cellularity than in RA, and somewhat greater vascularity. Some studies have indicated a higher tendency to synovial fibrosis in PsA. Unlike RA, PsA shows prominent enthesitis, with histology similar to that of the other spondyloarthritides.

PATHOGENESIS

PsA is almost certainly immune-mediated and probably shares pathogenic mechanisms with psoriasis. PsA synovium shows infiltration with T cells, B cells, macrophages, and NK receptor–expressing cells, with upregulation of leukocyte homing receptors. Clonally expanded CD8+ T cells are frequent in PsA. Plasmacytoid dendritic cells are thought to play a key role in psoriasis, and there is some evidence for their participation in psoriatic arthritis. There is abundant synovial overexpression of proinflammatory cytokines. Interleukin 2, interferon-γ, TNF-α, and IL-1β, -6, -8, -10, -12, -13, and -15 are found in PsA synovium or synovial fluid. T_H17 derived cytokines are likely to be important in PsA, given their prominence in psoriasis and in other spondyloarthritides, the genetic association with genes in the IL-12/IL-23 axis, and the therapeutic response to an antibody to the shared IL-12/23 p40 subunit (discussed later). Consistent with the extensive bone lesions in PsA, patients with PsA have been found to have a marked increase in osteoclastic precursors in peripheral blood and upregulation of receptor activator of nuclear factor κβ ligand (RANKL) in the synovial lining layer.

CLINICAL FEATURES

In 60–70% of cases, psoriasis precedes joint disease. In 15–20% of cases, the two manifestations appear within 1 year of each other. In about 15–20% of cases, the arthritis precedes the onset of psoriasis and can present a diagnostic challenge. The frequency in men and women is almost equal, although the frequency of disease patterns differs somewhat in the two sexes. The disease can begin in childhood or late in life but typically begins in the fourth or fifth decade, at an average age of 37 years.

The spectrum of arthropathy associated with psoriasis is quite broad. Many classification schemes have been proposed. In the original scheme of Wright and Moll, five patterns are described: (1) arthritis of the DIP joints; (2) asymmetric oligoarthritis; (3) symmetric polyarthritis similar to RA; (4) axial involvement (spine and sacroiliac joints); and (5) arthritis mutilans, a highly destructive form of disease. These patterns are not fixed, and the

pattern that persists chronically often differs from that of the initial presentation. A simpler scheme in recent use contains three patterns: oligoarthritis, polyarthritis, and axial arthritis.

Nail changes in the fingers or toes occur in 90% of patients with PsA, compared with 40% of psoriatic patients without arthritis, and pustular psoriasis is said to be associated with more severe arthritis. Several articular features distinguish PsA from other joint disorders. Dactylitis occurs in >30%; enthesitis and tenosynovitis are also common and are probably present in most patients, although often not appreciated on physical examination. Shortening of digits because of underlying osteolysis is particularly characteristic of PsA **(Fig. 10-3)**, and there is a much greater tendency than in RA for both fibrous and bony ankylosis of small joints. Rapid ankylosis of one or more proximal interphalangeal (PIP) joints early in the course of disease is not uncommon. Back and neck pain and stiffness are also common in PsA.

Arthropathy confined to the DIP joints predominates in about 15% of cases. Accompanying nail changes in the affected digits are almost always present. These joints are also often affected in the other patterns of PsA. Approximately 30% of patients have asymmetric oligoarthritis. This pattern commonly involves a knee or another large joint with a few small joints in the fingers or toes, often with dactylitis. Symmetric polyarthritis occurs in about 40% of PsA patients at presentation. It may be indistinguishable from RA in terms of the joints involved, but other features characteristic of PsA are usually also present. In general, peripheral joints in PsA tend to be somewhat less tender than in RA, although signs of inflammation are usually present. Almost any peripheral joint can be involved. Axial arthropathy without peripheral involvement is found in about 5% of PsA patients. It may be indistinguishable from idiopathic AS, although more neck involvement and less thoracolumbar spinal involvement is characteristic, and nail changes are not found in idiopathic AS. A small percentage of PsA patients have arthritis mutilans, in which there can be widespread shortening of digits ("telescoping"), sometimes coexisting with ankylosis and contractures in other digits.

Six patterns of nail involvement are identified: pitting, horizontal ridging, onycholysis, yellowish discoloration of the nail margins, dystrophic hyperkeratosis, and combinations of these findings. Other extraarticular manifestations of the spondyloarthritides are common. Eye involvement, either conjunctivitis or uveitis, is reported in 7–33% of PsA patients. Unlike the uveitis associated with AS, the uveitis in PsA is more often bilateral, chronic, and/or posterior. Aortic valve insufficiency has been found in <4% of patients, usually after long-standing disease.

Widely varying estimates of clinical outcome have been reported in PsA. At its worst, severe PsA with arthritis mutilans is at least as crippling and ultimately fatal as severe RA. Unlike RA, however, many patients with PsA experience temporary remissions. Overall, erosive disease develops in the majority of patients, progressive disease with deformity and disability is common, and in some large published series, mortality was found to be significantly increased compared with the general population.

The psoriasis and associated arthropathy seen with HIV infection both tend to be severe and can occur in populations with very little psoriasis in noninfected individuals. Severe enthesopathy, dactylitis, and rapidly progressive joint destruction are seen, but axial involvement is very rare. This condition is prevented by or responds well to antiretroviral therapy.



FIGURE 10-3
Characteristic lesions of psoriatic arthritis. Inflammation is prominent in the DIP joints (left 5th, 4th, 2nd; right 2nd, 3rd, and 5th) and PIP joints (left 2nd, right 2nd, 4th, and 5th). There is dactylitis in the left 2nd finger and thumb, with pronounced telescoping of the left 2nd finger. Nail dystrophy (hyperkeratosis and onycholysis) affects each of the fingers except the left 3rd finger, the only finger without arthritis. (*Courtesy of Donald Raddatz, MD; with permission.*)

LABORATORY AND RADIOGRAPHIC FINDINGS

There are no laboratory tests diagnostic of PsA. ESR and CRP are often elevated. A small percentage of patients may have low titers of rheumatoid factor or antinuclear antibodies. About 10% of patients have anti-CCP antibodies. Uric acid may be elevated in the presence of extensive psoriasis. HLA-B27 is found in 50–70% of patients with axial disease, but ≤20% in patients with only peripheral joint involvement.

The peripheral and axial arthropathies in PsA show a number of radiographic features that distinguish them from RA and AS, respectively. Characteristics of peripheral PsA include DIP involvement, including the classic "pencil-in-cup" deformity; marginal erosions with adjacent bony proliferation ("whiskering"); small-joint ankylosis; osteolysis of phalangeal and metacarpal bone, with telescoping of digits; and periostitis and proliferative new bone at sites of enthesitis. Characteristics of axial PsA include asymmetric sacroiliitis; compared with idiopathic AS, less zygapophyseal joint arthritis, fewer and less symmetric and delicate syndesmophytes; fluffy hyperperiostosis on anterior vertebral bodies; severe cervical spine involvement, with a tendency to atlantoaxial subluxation but relative sparing of the thoracolumbar spine; and paravertebral ossification. Ultrasound and MRI both readily demonstrate enthesitis and tendon sheath effusions that can be difficult to assess on physical examination. A recent MRI study of 68 PsA patients found sacroiliitis in 35%, unrelated to B27, but correlated with restricted spinal movement.

DIAGNOSIS

Classification criteria for PsA were published in 2006 [Classification of Psoriatic Arthritis (CASPAR) criteria] that have been widely accepted **(Table 10-2)**. The sensitivity and specificity of these criteria exceed 90%, and they are useful for early diagnosis. The criteria are based on the history, presence of psoriasis, characteristic peripheral or spinal joint symptoms, signs, and imaging. Diagnosis can be challenging when the arthritis precedes psoriasis, the psoriasis is undiagnosed or obscure, or the joint involvement closely resembles another form of arthritis. A high index of suspicion is needed in any patient with an undiagnosed inflammatory arthropathy. The history should include inquiry about psoriasis in the patient and family members. Patients should be asked to disrobe for the physical examination, and psoriasiform lesions should be sought in the scalp, ears, umbilicus, and gluteal folds in addition to more accessible sites; the finger and toe nails should also be carefully examined. Axial symptoms or signs, dactylitis, enthesitis, ankylosis, the pattern of joint involvement, and characteristic radiographic changes can be helpful clues. The differential diagnosis includes all other forms of arthritis, which can occur coincidentally in individuals with psoriasis. The differential diagnosis of isolated DIP involvement is short. Osteoarthritis (Heberden's nodes) is usually not inflammatory; gout involving more than one DIP joint often involves other sites and may be accompanied by tophi; the very rare entity multicentric reticulohistiocytosis involves other joints and has characteristic small pearly periungual skin nodules; and the uncommon entity inflammatory osteoarthritis, like the others, lacks the nail changes of PsA. Radiography can be helpful in all of these cases and in distinguishing between psoriatic spondylitis and idiopathic AS. A history of trauma to an affected joint preceding the onset of arthritis is said to occur more frequently in PsA than in other types of arthritis, perhaps reflecting the Koebner phenomenon in which psoriatic skin lesions can arise at sites of the skin trauma.

TABLE 10-2

THE CASPAR (CLASSIFICATION OF *PS*ORIATIC *AR*THRITIS) CRITERIA[a]

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from any of the following five categories:

1. Evidence of current psoriasis,[b, c] a personal history of psoriasis, or a family history of psoriasis[d]
2. Typical psoriatic nail dystrophy[e] observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis[f] or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation[g] in the hand or foot

[a]Specificity of 99% and sensitivity of 91%.
[b]Current psoriasis is assigned 2 points; all other features are assigned 1 point.
[c] Psoriatic skin or scalp disease present at the time of examination, as judged by a rheumatologist or dermatologist.
[d] History of psoriasis in a first- or second-degree relative.
[e]Onycholysis, pitting, or hyperkeratosis.
[f]Swelling of an entire digit.
[g]Ill-defined ossification near joint margins, excluding osteophyte formation.
Source: From W Taylor et al: Arthritis Rheum 54:2665, 2006.

TREATMENT **Psoriatic Arthritis**

Ideally, coordinated therapy is directed at both the skin and joints in PsA. As described earlier for AS, use of the anti-TNF-α agents has revolutionized the treatment of PsA. Prompt and dramatic resolution of both arthritis and skin lesions has been observed in large, randomized controlled trials of etanercept, infliximab, adalimumab, and golimumab. Many of the responding patients had long-standing disease that was resistant to all previous therapy, as well as extensive skin disease. The clinical response is more dramatic than in RA, and delay of disease progression has been demonstrated radiographically. Paradoxically, rare cases have been

reported of exacerbation or de novo appearance of psoriasis precipitated by anti-TNF therapy for a variety of conditions. In some cases, the therapy can nevertheless be continued.

Ustekinumab, a monoclonal antibody to the shared IL-23/IL-12p40 subunit, has been approved by FDA for treating moderate to severe plaque psoriasis.

Other treatment for PsA has been based on drugs that have efficacy in RA and/or in psoriasis. Although methotrexate in doses of 15–25 mg/week and sulfasalazine (usually given in doses of 2–3 g/d) have each been found to have clinical efficacy in controlled trials, neither effectively halts progression of erosive joint disease. Other agents with efficacy in psoriasis reported to benefit PsA are cyclosporine, retinoic acid derivatives, and psoralens plus ultraviolet A light (PUVA). There is controversy regarding the efficacy in PsA of gold and antimalarials, which have been widely used in RA. The pyrimidine synthetase inhibitor leflunomide has been shown in a randomized controlled trial to be beneficial in both psoriasis and psoriatic arthritis.

All of these treatments require careful monitoring. Immunosuppressive therapy may be used cautiously in HIV-associated PsA if the HIV infection is well controlled.

In one large prospective series, 7% of patients with PsA required musculoskeletal surgery beginning at a mean of 13 years' disease duration. Indications for surgery are similar to those in RA, although there is an impression that outcomes in PsA may be less satisfactory.

UNDIFFERENTIATED AND JUVENILE-ONSET SPONDYLOARTHRITIS

Many patients, usually young adults, present with some features of one or more of the spondyloarthritides discussed earlier. Until recently, these patients were said to have undifferentiated spondyloarthritis, or simply spondyloarthritis, as defined by the 1991 European Spondyloarthropathy Study Group criteria **(Table 10-3)**. For example, a patient may present with inflammatory synovitis of one knee, Achilles tendinitis, and dactylitis of one digit. Some of these patients may have ReA in which the triggering infection remains clinically silent. In some other cases, the patient subsequently develops IBD or psoriasis or the process eventually meets criteria for AS. This diagnosis of undifferentiated SpA was also commonly applied to patients with inflammatory back pain, who did meet modified New York criteria for AS. Most of these would now be classified under the new category of axial spondyloarthritis (Table 10-1).

Approximately one-half of the patients with undifferentiated SpA are HLA-B27-positive, and thus the absence of B27 is not useful in establishing or excluding the diagnosis. In familial cases, which are much more frequently B27-positive, there is often eventual progression to classical AS.

In juvenile-onset SpA, which begins between ages 7 and 16, most commonly in boys (60–80%), an asymmetric, predominantly lower-extremity oligoarthritis and enthesitis without extraarticular features is the typical mode of presentation. The prevalence of B27 in this

TABLE 10-3

EUROPEAN SPONDYLOARTHROPATHY STUDY GROUP (ESSG) CRITERIA FOR SPONDYLOARTHRITIS[A]

		SYNOVITIS
INFLAMMATORY BACK PAIN[B]	***OR***	• **ASYMMETRIC *OR***
		• **PREDOMINANTLY IN LOWER EXTREMITIES**
	AND	

One or more of the following:
- Family history of SpA[b]
- Psoriasis[b]
- Crohn's disease or ulcerative colitis[c]
- Nongonococcal urethritis, cervicitis, or acute diarrhea within 1 month before arthritis
- Alternating buttock pain[d]
- Enthesitis[b]
- Radiographic sacroiliitis[b]

[a]Sensitivity >85%, specificity >85%.
[b]See definition in Table 10-1.
[c]Past or present, diagnosed by a physician and confirmed by endoscopy or radiography.
[d]Past or present pain alternating between the right and left gluteal regions.
SpA, spondyloarthritis.
Source: From M Dougados et al: Arthritis Rheum 34:1218, 1991; J Sieper et al: Ann Rheum Dis 68:ii1, 2009. Copyright 2009, with permission from BMJ Publishing Group Ltd.

condition, which has been termed the *seronegative enthesopathy and arthropathy (SEA) syndrome*, is approximately 80%. Many, but not all, of these patients go on to develop AS in late adolescence or adulthood.

Management of undifferentiated SpA is similar to that of the other spondyloarthritides. Response to anti-TNF-α therapy has been documented, and this therapy is indicated in severe, persistent cases not responsive to other treatment. One 2004 publication reported significant benefit in patients with long-standing undifferentiated spondyloarthropathy treated for 9 months with doxycycline and rifampin. These data await confirmation.

Current pediatric textbooks and journals should be consulted for information on management of juvenile-onset SpA.

ENTEROPATHIC ARTHRITIS

HISTORIC BACKGROUND

A relationship between arthritis and IBD was observed in the 1930s. The relationship was further defined by the epidemiologic studies in the 1950s and 1960s and included in the concept of the spondyloarthritides in the 1970s.

EPIDEMIOLOGY

Both of the common forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD), are associated with SpA. UC and CD both have an estimated prevalence of 0.05–0.1%, and the incidence of each is thought to have increased in recent decades. AS and peripheral arthritis are both associated with UC and with CD. Wide variations have been reported in the estimated frequencies of these associations. In recent series, AS was diagnosed in 1–10%, and peripheral arthritis in 10–50% of patients with IBD. Inflammatory back pain and enthesopathy are common, and many patients have sacroiliitis on imaging studies.

The prevalence of UC or CD in patients with AS is thought to be 5–10%. However, investigation of unselected SpA patients by ileocolonoscopy has revealed that from one-third to two-thirds of patients with AS have subclinical intestinal inflammation that is evident either macroscopically or histologically. These lesions have also been found in patients with undifferentiated SpA or ReA (both enterically and urogenitally acquired).

Both UC and CD have a tendency to familial aggregation, more so for CD. HLA associations have been weak and inconsistent. HLA-B27 is found in up to 70% of patients with IBD and AS, but in ≤15% of patients with IBD and peripheral arthritis or IBD alone. Three alleles of the *NOD2/CARD15* gene on chromosome 16 have been found in approximately one-half of patients with CD. These alleles are not associated with the spondyloarthritides per se. However, they are found significantly more often in (1) CD patients with sacroiliitis than in those without sacroiliitis, and (2) SpA patients with chronic inflammatory gut lesions than in those with normal gut histology. These associations are independent of HLA-B27.

Genome studies have shown that CD and UC have some susceptibility genes in common and some specific to each condition. Among these, IL-23R (highly associated with CD and to a lesser degree with UC) is shared with AS and psoriasis. TNFSF15, associated with CD, has also been found linked to SpA.

PATHOLOGY

Available data for IBD-associated peripheral arthritis suggest a synovial histology similar to other spondyloarthritides. Association with arthropathy does not affect the gut histology of UC or CD. The subclinical inflammatory lesions in the colon and distal ileum associated with SpA have been classified as either acute or chronic. The former resemble acute bacterial enteritis, with largely intact architecture and neutrophilic infiltration in the lamina propria. The latter resemble the lesions of CD, with distortion of villi and crypts, aphthoid ulceration, and mononuclear cell infiltration in the lamina propria.

PATHOGENESIS

Both IBD and SpA are immune-mediated, but the specific pathogenic mechanisms are poorly understood, and the connection between the two is obscure. The shared genetics could reflect either shared pathogenetic mechanisms, close genetic linkage of separate susceptibility alleles, or both. IBD is a common phenotype in a number of rodent lines with transgenic overexpression or targeted deletion of genes involved in immune processes. Arthritis is an accompanying prominent feature in two of these IBD models, B27 transgenic rats and mice with constitutive overexpression of TNF-α, and immune dysregulation is prominent in both. Several lines of evidence indicate trafficking of leukocytes between the gut and the joint. Mucosal leukocytes from IBD patients have been shown to bind avidly to synovial vasculature through several different adhesion molecules. Macrophages expressing CD163 are prominent in the inflammatory lesions of both gut and synovium in the spondyloarthritides.

CLINICAL FEATURES

AS associated with IBD is clinically indistinguishable from idiopathic AS. It runs a course independent of the bowel disease, and in many patients it precedes

the onset of IBD, sometimes by many years. Peripheral arthritis not infrequently begins before onset of overt bowel disease. The spectrum of peripheral arthritis includes acute self-limited attacks of oligoarthritis that often coincide with relapses of IBD, and more chronic and symmetric polyarticular arthritis that runs a course independent of IBD activity. The patterns of joint involvement are similar in UC and CD. In general, erosions and deformities are infrequent in IBD-associated peripheral arthritis, and joint surgery is infrequently required. Isolated destructive hip arthritis is a rare complication of CD, apparently distinct from osteonecrosis and septic arthritis. Dactylitis and enthesopathy are occasionally found. In addition to the ~20% of IBD patients with SpA, a comparable percentage have arthralgias or fibromyalgia symptoms.

Other extraintestinal manifestations of IBD are seen in addition to arthropathy, including uveitis, pyoderma gangrenosum, erythema nodosum, and finger clubbing, all somewhat more commonly in CD than UC. The uveitis shares the features described earlier for PsA-associated uveitis.

LABORATORY AND RADIOGRAPHIC FINDINGS

Laboratory findings reflect the inflammatory and metabolic manifestations of IBD. Joint fluid is usually at least mildly inflammatory. Of patients with AS and IBD, 30–70% carry the HLA-B27 gene, compared with >90% of patients with AS alone and 50–70% of those with AS and psoriasis. Hence, definite or probable AS in a B27-negative individual in the absence of psoriasis should prompt a search for occult IBD. Radiographic changes in the axial skeleton are the same as in uncomplicated AS. Erosions are uncommon in peripheral arthritis but may occur, particularly in the metatarsophalangeal joints. Isolated destructive hip disease has been described.

DIAGNOSIS

Diarrhea and arthritis are both common conditions that can coexist for a variety of reasons. When etiopathogenically related, reactive arthritis and IBD-associated arthritis are the most common causes. Rare causes include celiac disease, blind loop syndromes, and Whipple's disease. In most cases, diagnosis depends upon investigation of the bowel disease.

TREATMENT **Enteropathic Arthritis**

Treatment of CD has been improved by therapy with anti-TNF agents. Infliximab and adalimumab are effective for induction and maintenance of clinical remission in CD, and infliximab has been shown to be effective in fistulizing CD. IBD-associated arthritis also responds to these agents. Other treatment for IBD, including sulfasalazine and related drugs, systemic glucocorticoids, and immunosuppressive drugs, are also usually of benefit for associated peripheral arthritis. NSAIDs are generally helpful and well tolerated, but they can precipitate flares of IBD. Rare cases of IBD, usually UC, have apparently been precipitated by anti-TNF therapy, usually etanercept, given for any of several rheumatic diseases.

SAPHO SYNDROME

The syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) is characterized by a variety of skin and musculoskeletal manifestations. Dermatologic manifestations include palmoplantar pustulosis, acne conglobata, acne fulminans, and hidradenitis suppurativa. The main musculoskeletal findings are sternoclavicular and spinal hyperostosis, chronic recurrent foci of sterile osteomyelitis, and axial or peripheral arthritis. Cases with one or a few manifestations are probably the rule. The ESR is usually elevated, sometimes dramatically. In some cases, bacteria, most often *Propionibacterium acnes*, have been cultured from bone biopsy specimens and occasionally other sites. Inflammatory bowel disease was coexistent in 8% of patients in one large series. B27 is not associated. Either bone scan or CT scan is helpful diagnostically. A recent MRI report described a characteristic vertebral body corner cortical erosions in 12 out of 12 patients. High-dose NSAIDs may provide relief from bone pain. A number of uncontrolled series and case reports describe successful therapy with pamidronate or other bisphosphonates. Response to anti-TNF-α therapy has also been observed, although in a few cases this has been associated with a flare of skin manifestations. Successful prolonged antibiotic therapy has also been reported.

WHIPPLE'S DISEASE

Whipple's disease is a rare chronic bacterial infection, mostly of middle-aged white men, caused by *Tropheryma whipplei*. At least 75% of affected individuals develop an oligo- or polyarthritis. The joint manifestations usually precede other symptoms of the disease by 5 years or more; they are thus particularly important because appropriate antibiotic therapy is curative, whereas the untreated disease is fatal. Large and small peripheral joints and sacroiliac joints may be involved. The arthritis is abrupt in onset, migratory, usually lasts hours to a few days, and then resolves completely. Chronic

polyarthritis can occur but is not typical. Eventually prolonged diarrhea, malabsorption, and weight loss occur. Other manifestations of systemic disease include fever, edema, serositis, endocarditis, pneumonia, hypotension, lymphadenopathy, hyperpigmentation, subcutaneous nodules, clubbing, and uveitis. Central nervous system involvement eventually develops in 80% of untreated patients, with cognitive changes, headache, diplopia, and papilledema, and may be detectable on MRI. Oculomasticatory and oculofacial-skeletal myorhythmia with supranuclear vertical gaze palsy are said to be pathognomonic. Laboratory abnormalities include anemia and changes from malabsorption. Synovial fluid is usually inflammatory. Radiography rarely shows joint erosions but may show sacroiliitis. Abdominal CT may reveal lymphadenopathy. Foamy macrophages containing periodic acid–Schiff (PAS)-staining bacterial remnants can be seen in biopsies of small intestine, synovium, lymph node, and other tissues.

The complete genome sequence of *T. whipplei* was published in 2003. Diagnosis is facilitated by PCR amplification of sequences of the 16S ribosomal gene or other genes of *T. whipplei* in biopsied tissue. In the future, this may be supplanted or complemented by serologic tests. The organism is ubiquitous in the environment and is found in some healthy individuals, so the mere presence of DNA does not establish a diagnosis. The syndrome responds to therapy with penicillin (or ceftriaxone) and streptomycin for 2 weeks followed by trimethoprim-sulfamethoxazole for 1–2 years, but other antibiotic regimens may be preferable, and infectious disease consultation is strongly advised. Monitoring for central nervous system relapse is critical. Recently, nonclassical infections with *T. whipplei* have been described, including endocarditis.

CHAPTER 11

THE VASCULITIS SYNDROMES

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DEFINITION

Vasculitis is a clinicopathologic process characterized by inflammation of and damage to blood vessels. The vessel lumen is usually compromised, and this is associated with ischemia of the tissues supplied by the involved vessel. A broad and heterogeneous group of syndromes may result from this process, since any type, size, and location of blood vessel may be involved. Vasculitis and its consequences may be the primary or sole manifestation of a disease; alternatively, vasculitis may be a secondary component of another primary disease. Vasculitis may be confined to a single organ, such as the skin, or it may simultaneously involve several organ systems.

CLASSIFICATION

A major feature of the vasculitic syndromes as a group is the fact that there is a great deal of heterogeneity at the same time as there is considerable overlap among them. This heterogeneity and overlap in addition to a lack of understanding of the pathogenesis of these syndromes have been major impediments to the development of a coherent classification system for these diseases. Table 11-1 lists the major vasculitis syndromes. The distinguishing and overlapping features of these syndromes are discussed next.

TABLE 11-1

VASCULITIS SYNDROMES

PRIMARY VASCULITIS SYNDROMES	SECONDARY VASCULITIS SYNDROMES
Granulomatosis with polyangiitis (Wegener's)	Drug-induced vasculitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Serum sickness
Polyarteritis nodosa	Vasculitis associated with other primary diseases
Microscopic polyangiitis	Infection
Giant cell arteritis	Malignancy
Takayasu arteritis	Rheumatic disease
IgA vasculitis (Henoch-Schönlein)	
Idiopathic cutaneous vasculitis	
Cryoglobulinemic vasculitis	
Behçet's disease	
Primary central nervous system vasculitis	
Cogan's syndrome	
Kawasaki disease	

PATHOPHYSIOLOGY AND PATHOGENESIS

Generally, most of the vasculitic syndromes are assumed to be mediated at least in part by immunopathogenic mechanisms that occur in response to certain antigenic stimuli (Table 11-2). However, evidence supporting this hypothesis is for the most part indirect and may reflect epiphenomena as opposed to true causality. Furthermore, it is unknown why some individuals might develop vasculitis in response to certain antigenic stimuli, whereas others do not. It is likely that a number of factors are involved in the ultimate expression of a vasculitic syndrome. These include the genetic predisposition, environmental exposures, and the regulatory mechanisms associated with immune response to certain antigens.

PATHOGENIC IMMUNE-COMPLEX FORMATION

Vasculitis is generally considered within the broader category of *immune-complex diseases* that include serum sickness and certain of the connective tissue diseases, of which systemic lupus erythematosus (Chap. 4) is the

TABLE 11-2

POTENTIAL MECHANISMS OF VESSEL DAMAGE IN VASCULITIS SYNDROMES
Pathogenic immune complex formation and/or deposition
Henoch-Schönlein purpura
Vasculitis associated with collagen vascular diseases
Serum sickness and cutaneous vasculitis syndromes
Hepatitis C–associated cryoglobulinemic vasculitis
Polyarteritis nodosa–like vasculitis associated with hepatitis B
Production of antineutrophil cytoplasmic antibodies
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Microscopic polyangiitis
Pathogenic T lymphocyte responses and granuloma formation
Giant cell arteritis
Takayasu arteritis
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Source: Adapted from MC Sneller, AS Fauci: Med Clin North Am 81:221, 1997.

prototype. Although deposition of immune complexes in vessel walls is the most widely accepted pathogenic mechanism of vasculitis, the causal role of immune complexes has not been clearly established in most of the vasculitic syndromes. Circulating immune complexes need not result in deposition of the complexes in blood vessels with ensuing vasculitis, and many patients with active vasculitis do not have demonstrable circulating or deposited immune complexes. The actual antigen contained in the immune complex has only rarely been identified in vasculitic syndromes. In this regard, hepatitis B antigen has been identified in both the circulating and deposited immune complexes in a subset of patients who have features of a systemic vasculitis, most notably in polyarteritis nodosa (PAN; see "Polyarteritis Nodosa"). Cryoglobulinemic vasculitis is strongly associated with hepatitis C virus infection; hepatitis C virions and hepatitis C virus antigen-antibody complexes have been identified in the cryoprecipitates of these patients (see "Cryoglobulinemic Vasculitis").

The mechanisms of tissue damage in immune complex–mediated vasculitis resemble those described for serum sickness. In this model, antigen-antibody complexes are formed in antigen excess and are deposited in vessel walls whose permeability has been increased by vasoactive amines such as histamine, bradykinin, and leukotrienes released from platelets or from mast cells as a result of IgE-triggered mechanisms. The deposition of complexes results in activation of complement components, particularly C5a, which is strongly chemotactic for neutrophils. These cells then infiltrate the vessel wall, phagocytose the immune complexes, and release their intracytoplasmic enzymes, which damage the vessel wall. As the process becomes subacute or chronic, mononuclear cells infiltrate the vessel wall. The common denominator of the resulting syndrome is compromise of the vessel lumen with ischemic changes in the tissues supplied by the involved vessel. Several variables may explain why only certain types of immune complexes cause vasculitis and why only certain vessels are affected in individual patients. These include the ability of the reticuloendothelial system to clear circulating complexes from the blood, the size and physicochemical properties of immune complexes, the relative degree of turbulence of blood flow, the intravascular hydrostatic pressure in different vessels, and the preexisting integrity of the vessel endothelium.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

ANCA are antibodies directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes. These autoantibodies are present in a high percentage of patients with active granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis, and in a lower percentage of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Because these diseases share the presence of ANCA and small-vessel vasculitis, some investigators have come to refer to them collectively as "ANCA-associated vasculitis." However, as these diseases possess unique clinical phenotypes in which ANCA may be absent, it remains our opinion that granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) should continue to be viewed as separate entities.

There are two major categories of ANCA based on different targets for the antibodies. The terminology of *cytoplasmic ANCA* (cANCA) refers to the diffuse, granular cytoplasmic staining pattern observed by immunofluorescence microscopy when serum antibodies bind to indicator neutrophils. Proteinase-3, a 29-kDa neutral serine proteinase present in neutrophil azurophilic granules, is the major cANCA antigen. More than 90% of patients with typical active granulomatosis with polyangiitis (Wegener's) have detectable antibodies to proteinase-3 (see next). The terminology of *perinuclear ANCA* (pANCA) refers to the more localized perinuclear or nuclear staining pattern of the indicator neutrophils. The major target for pANCA is the enzyme myeloperoxidase; other targets that can produce a pANCA pattern of staining include elastase, cathepsin G, lactoferrin, lysozyme, and bactericidal/permeability-increasing protein. However, only antibodies to myeloperoxidase have been convincingly associated with vasculitis. Antimyeloperoxidase antibodies have been reported to occur in variable

percentages of patients with microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), crescentic glomerulonephritis, and granulomatosis with polyangiitis (Wegener's) (see later). A pANCA pattern of staining that is not due to antimyeloperoxidase antibodies has been associated with nonvasculitic entities such as rheumatic and nonrheumatic autoimmune diseases, inflammatory bowel disease, certain drugs, and infections such as endocarditis and bacterial airway infections in patients with cystic fibrosis.

It is unclear why patients with these vasculitis syndromes develop antibodies to myeloperoxidase or proteinase-3, whereas such antibodies are rare in other inflammatory diseases and autoimmune diseases. It is also unclear what role these antibodies play in disease pathogenesis. There are a number of in vitro observations that suggest possible mechanisms whereby these antibodies can contribute to the pathogenesis of the vasculitis syndromes. Proteinase-3 and myeloperoxidase reside in the azurophilic granules and lysosomes of resting neutrophils and monocytes, where they are apparently inaccessible to serum antibodies. However, when neutrophils or monocytes are primed by tumor necrosis factor α (TNF-α) or interleukin 1 (IL-1), proteinase-3 and myeloperoxidase translocate to the cell membrane, where they can interact with extracellular ANCA. The neutrophils then degranulate and produce reactive oxygen species that can cause tissue damage. Furthermore, ANCA-activated neutrophils can adhere to and kill endothelial cells in vitro. Activation of neutrophils and monocytes by ANCA also induces the release of proinflammatory cytokines such as IL-1 and IL-8. Recent adoptive transfer experiments in genetically engineered mice provide further evidence for a direct pathogenic role of ANCA in vivo. In contradiction, however, a number of clinical and laboratory observations argue against a primary pathogenic role for ANCA. Patients may have active granulomatosis with polyangiitis (Wegener's) in the absence of ANCA; the absolute height of the antibody titers does not correlate well with disease activity; and patients with granulomatosis with polyangiitis (Wegener's) in remission may continue to have high antiproteinase-3 (cANCA) titers for years (see next). Thus, the role of these autoantibodies in the pathogenesis of systemic vasculitis remains unclear.

PATHOGENIC T LYMPHOCYTE RESPONSES AND GRANULOMA FORMATION

In addition to the classic immune complex–mediated mechanisms of vasculitis as well as ANCA, other immunopathogenic mechanisms may be involved in damage to vessels. The most prominent of these are delayed hypersensitivity and cell-mediated immune injury as reflected in the histopathologic feature of granulomatous vasculitis. However, immune complexes themselves may induce granulomatous responses. Vascular endothelial cells can express HLA class II molecules following activation by cytokines such as interferon (IFN) γ. This allows these cells to participate in immunologic reactions such as interaction with CD4+ T lymphocytes in a manner similar to antigen-presenting macrophages. Endothelial cells can secrete IL-1, which may activate T lymphocytes and initiate or propagate in situ immunologic processes within the blood vessel. In addition, IL-1 and TNF-α are potent inducers of endothelial-leukocyte adhesion molecule 1 (ELAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which may enhance the adhesion of leukocytes to endothelial cells in the blood vessel wall. Other mechanisms such as direct cellular cytotoxicity, antibody directed against vessel components, or antibody-dependent cellular cytotoxicity have been suggested in certain types of vessel damage. However, there is no convincing evidence to support their causal contribution to the pathogenesis of any of the recognized vasculitic syndromes.

APPROACH TO THE PATIENT — General Principles of Diagnosis

The diagnosis of vasculitis is often considered in any patient with an unexplained systemic illness. However, there are certain clinical abnormalities that when present alone or in combination should suggest a diagnosis of vasculitis. These include palpable purpura, pulmonary infiltrates and microscopic hematuria, chronic inflammatory sinusitis, mononeuritis multiplex, unexplained ischemic events, and glomerulonephritis with evidence of multisystem disease. A number of nonvasculitic diseases may also produce some or all of these abnormalities. Thus, the first step in the workup of a patient with suspected vasculitis is to exclude other diseases that produce clinical manifestations that can mimic vasculitis (Table 11-3). It is particularly important to exclude infectious diseases with features that overlap those of vasculitis, especially if the patient's clinical condition is deteriorating rapidly and empirical immunosuppressive treatment is being contemplated.

Once diseases that mimic vasculitis have been excluded, the workup should follow a series of progressive steps that establish the diagnosis of vasculitis and determine, where possible, the category of the vasculitis syndrome (Fig. 11-1). This approach is of considerable importance since several of the vasculitis syndromes require aggressive therapy with glucocorticoids and cytotoxic agents, while other syndromes usually resolve spontaneously and require symptomatic treatment only. The definitive diagnosis of vasculitis is made upon biopsy of involved tissue. The yield of "blind" biopsies of organs with no subjective or objective evidence of involvement is very low and should be avoided. When

TABLE 11-3

CONDITIONS THAT CAN MIMIC VASCULITIS

- Infectious diseases
 - Bacterial endocarditis
 - Disseminated gonococcal infection
 - Pulmonary histoplasmosis
 - Coccidioidomycosis
 - Syphilis
 - Lyme disease
 - Rocky Mountain spotted fever
 - Whipple's disease
- Coagulopathies/thrombotic microangiopathies
 - Antiphospholipid antibody syndrome
 - Thrombotic thrombocytopenic purpura
- Neoplasms
 - Atrial myxoma
 - Lymphoma
 - Carcinomatosis
- Drug toxicity
 - Cocaine
 - Levamisole
 - Amphetamines
 - Ergot alkaloids
 - Methysergide
 - Arsenic
- Sarcoidosis
- Atheroembolic disease
- Antiglomerular basement membrane disease (Goodpasture's syndrome)
- Amyloidosis
- Migraine

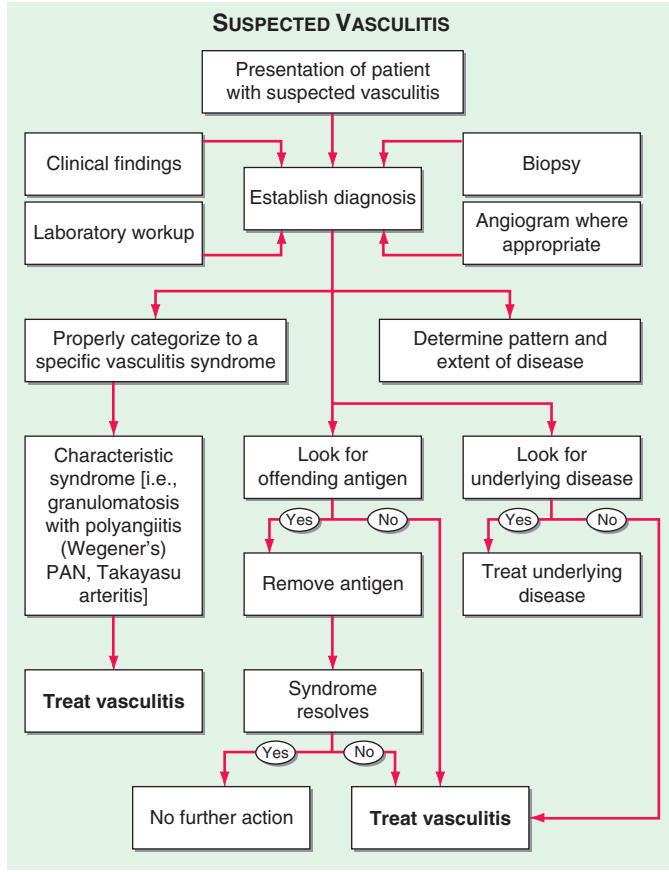


FIGURE 11-1

Algorithm for the approach to a patient with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

syndromes such as PAN, Takayasu arteritis, or primary central nervous system (CNS) vasculitis are suspected, arteriogram of organs with suspected involvement should be performed. However, arteriograms should not be performed routinely when patients present with localized cutaneous vasculitis with no clinical indication of visceral involvement.

GENERAL PRINCIPLES OF TREATMENT Once a diagnosis of vasculitis has been established, a decision regarding therapeutic strategy must be made (Fig. 11-1). If an offending antigen that precipitates the vasculitis is recognized, the antigen should be removed where possible. If the vasculitis is associated with an underlying disease such as an infection, neoplasm, or connective tissue disease, the underlying disease should be treated. If the syndrome represents a primary vasculitic disease, treatment should be initiated according to the category of the vasculitis syndrome. Specific therapeutic regimens are discussed next for the individual vasculitis syndromes; however, certain general principles regarding therapy should be considered. Decisions regarding treatment should be based upon the use of regimens for which there has been published literature supporting efficacy for that particular vasculitic disease. Since the potential toxic side effects of certain therapeutic regimens may be substantial, the risk-versus-benefit ratio of any therapeutic approach should be weighed carefully. On the one hand, glucocorticoids and/or cytotoxic therapy should be instituted immediately in diseases where irreversible organ system dysfunction and high morbidity and mortality rates have been clearly established. Granulomatosis with polyangiitis (Wegener's) is the prototype of a severe systemic vasculitis requiring such a therapeutic approach (see next). On the other hand, when feasible, aggressive therapy should be avoided for vasculitic manifestations that rarely result in irreversible organ system dysfunction and that usually do not respond to such therapy. For example, idiopathic cutaneous vasculitis usually resolves with symptomatic treatment, and prolonged courses of glucocorticoids uncommonly result in clinical benefit. Cytotoxic agents have not proved to be beneficial in idiopathic cutaneous vasculitis, and their toxic side effects generally outweigh any potential beneficial effects. Glucocorticoids should be initiated in those systemic vasculitides that cannot be specifically categorized or for which there is no established

standard therapy; cytotoxic therapy should be added in these diseases only if an adequate response does not result or if remission can only be achieved and maintained with an unacceptably toxic regimen of glucocorticoids. When remission is achieved, one should continually attempt to taper glucocorticoids and discontinue when possible. When using cytotoxic regimens, one should base the choice of agent upon the available therapeutic data supporting efficacy in that disease, the site and severity of organ involvement, and the toxicity profile of the drug.

Physicians should be thoroughly aware of the toxic side effects of therapeutic agents employed that can include both acute and long-term complications (Table 11-4). Morbidity and mortality can occur as a result of treatment and strategies to monitor for and prevent toxicity represent an essential part of patient care. Glucocorticoids are an important part of treatment for most vasculitides but are associated with substantial toxicities. Monitoring and prevention of glucocorticoid-induced bone loss is important in all patients. With the use of daily cyclophosphamide, strategies are particularly important and are directed toward minimization of bladder toxicity and prevention of leukopenia. Instructing the patient to take cyclophosphamide all at once in the morning with a large amount of fluid throughout the day in order to maintain a dilute urine can reduce the risk of bladder injury. Bladder cancer can occur several years after discontinuation of cyclophosphamide therapy; therefore, monitoring for bladder cancer should continue indefinitely in patients who have received cyclophosphamide. Bone marrow suppression is an important toxicity of cyclophosphamide and can be observed during glucocorticoid tapering or over time, even after periods of stable measurements. Monitoring of the complete blood count every 1–2 weeks for as long as the patient receives cyclophosphamide can effectively prevent cytopenias. Maintaining the white blood count (WBC) at >3000/μL and the neutrophil count >1500/μL is essential to reduce the risk of life-threatening infections.

Methotrexate and azathioprine are also associated with bone marrow suppression, and complete blood counts should be obtained every 1–2 weeks for the first 1–2 months after their initiation and once a month thereafter. To lessen toxicity, methotrexate is often given together with folic acid, 1 mg daily, or folinic acid, 5–10 mg once a week 24 h following methotrexate. Prior to initiation of azathioprine, thiopurine methyltransferase (TPMT), an enzyme involved in the metabolism of azathioprine, should be assayed because inadequate levels may result in severe cytopenia.

Infection represents a significant toxicity for all vasculitis patients treated with immunosuppressive therapy. Infections with *Pneumocystis jiroveci* and certain fungi can be seen even in the face of WBCs that are within normal limits, particularly in patients receiving glucocorticoids. All vasculitis patients who are receiving daily glucocorticoids in combination with a cytotoxic drug should receive trimethoprim-sulfamethoxazole (TMP-SMX) or another prophylactic therapy to prevent *P. jiroveci* infection.

Finally, it should be emphasized that each patient is unique and requires individual decision-making. The earlier outline should serve as a framework to guide therapeutic approaches; however, flexibility should be practiced in order to provide maximal therapeutic efficacy with minimal toxic side effects in each patient.

TABLE 11-4

MAJOR TOXIC SIDE EFFECTS OF CONVENTIONAL IMMUNOSUPPRESSIVE AGENTS COMMONLY USED IN THE TREATMENT OF SYSTEMIC VASCULITIS

Glucocorticoids	
Osteoporosis	Growth suppression in children
Cataracts	Hypertension
Glaucoma	Avascular necrosis of bone
Diabetes mellitus	Myopathy
Electrolyte abnormalities	Alterations in mood
Metabolic abnormalities	Psychosis
Suppression of inflammatory and immune responses leading to opportunistic infections	Pseudotumor cerebri
	Peptic ulcer diathesis
	Pancreatitis
Cushingoid features	
Cyclophosphamide	
Bone marrow suppression	Hypogammaglobulinemia
Cystitis	Pulmonary fibrosis
Bladder carcinoma	Myelodysplasia
Gonadal suppression	Oncogenesis
Gastrointestinal intolerance	Teratogenicity
	Opportunistic infections
Methotrexate	
Gastrointestinal intolerance	Pneumonitis
Stomatitis	Teratogenicity
Bone marrow suppression	Opportunistic infections
Hepatotoxicity (may lead to fibrosis or cirrhosis)	
Azathioprine	
Gastrointestinal intolerance	Opportunistic infections
Bone marrow suppression	Hypersensitivity
Hepatotoxicity	

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)

DEFINITION

Granulomatosis with polyangiitis (Wegener's) is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving both small arteries and veins may occur.

INCIDENCE AND PREVALENCE

Granulomatosis with polyangiitis (Wegener's) is an uncommon disease with an estimated prevalence of 3 per 100,000. It is extremely rare in blacks compared with whites; the male-to-female ratio is 1:1. The disease can be seen at any age; ~15% of patients are <19 years of age, but only rarely does the disease occur before adolescence; the mean age of onset is ~40 years.

PATHOLOGY AND PATHOGENESIS

The histopathologic hallmarks of granulomatosis with polyangiitis (Wegener's) are necrotizing vasculitis of small arteries and veins together with granuloma formation, which may be either intravascular or extravascular **(Fig. 11-2)**. Lung involvement typically appears as multiple, bilateral, nodular cavitary infiltrates **(Fig. 11-3)**, which on biopsy almost invariably reveal the typical necrotizing granulomatous vasculitis. Upper airway lesions, particularly those in the sinuses and nasopharynx, typically reveal inflammation, necrosis, and granuloma formation, with or without vasculitis.

In its earliest form, renal involvement is characterized by a focal and segmental glomerulitis that may evolve into a rapidly progressive crescentic glomerulonephritis. Granuloma formation is only rarely seen on renal biopsy. In contrast to other forms of glomerulonephritis, evidence of immune complex deposition is not found in the renal lesion of granulomatosis with polyangiitis (Wegener's). In addition to the classic triad of disease of the upper and lower respiratory tracts and kidney, virtually any organ can be involved with vasculitis, granuloma, or both.

The immunopathogenesis of this disease is unclear, although the involvement of upper airways and lungs with granulomatous vasculitis suggests an aberrant cell-mediated immune response to an exogenous or even endogenous antigen that enters through or resides in the upper airway. Chronic nasal carriage of *Staphylococcus aureus* has been reported to be associated with a higher relapse rate of granulomatosis with polyangiitis (Wegener's); however, there is no evidence for a role of this organism in the pathogenesis of the disease.

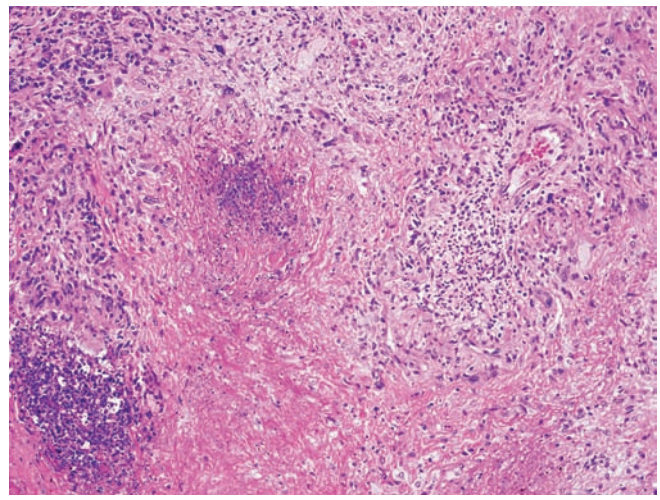


FIGURE 11-2
Lung histology in granulomatosis with polyangiitis (Wegener's). This area of geographic necrosis has a serpiginous border of histiocytes and giant cells surrounding a central necrotic zone. Vasculitis is also present with neutrophils and lymphocytes infiltrating the wall of a small arteriole *(upper right).* (*Courtesy of William D. Travis, MD; with permission.*)

Peripheral blood mononuclear cells obtained from patients with granulomatosis with polyangiitis (Wegener's) manifest increased secretion of IFN-γ but not of IL-4, IL-5, or IL-10 compared to normal controls. In addition, TNF-α production from peripheral blood mononuclear cells and CD4+ T cells is elevated. Furthermore, monocytes from patients with granulomatosis with polyangiitis (Wegener's) produce increased amounts of IL-12. These findings indicate an unbalanced T_H1-type T cell cytokine pattern in this disease that may have pathogenic and perhaps ultimately therapeutic implications.

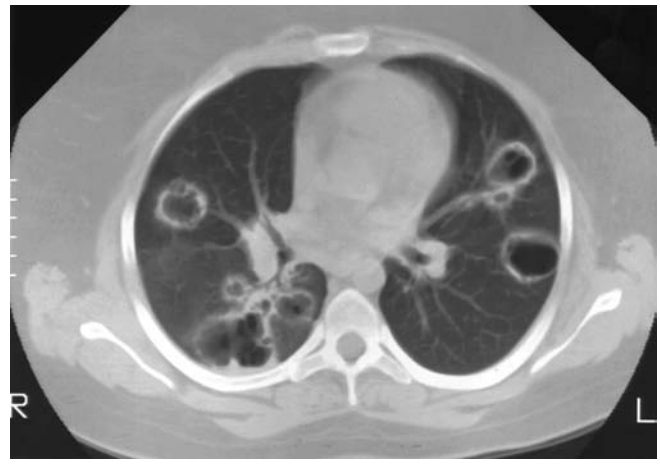


FIGURE 11-3
Computed tomography scan of a patient with granulomatosis with polyangiitis (Wegener's). The patient developed multiple, bilateral, and cavitary infiltrates.

A high percentage of patients with granulomatosis with polyangiitis (Wegener's) develop ANCA, and these autoantibodies may play a role in the pathogenesis of this disease (see earlier).

CLINICAL AND LABORATORY MANIFESTATIONS

Involvement of the upper airways occurs in 95% of patients with granulomatosis with polyangiitis (Wegener's). Patients often present with severe upper respiratory tract findings such as paranasal sinus pain and drainage and purulent or bloody nasal discharge, with or without nasal mucosal ulceration **(Table 11-5)**. Nasal septal perforation may follow, leading to saddle nose deformity. Serous otitis media may occur as a result of eustachian tube blockage. Subglottic tracheal stenosis resulting from active disease or scarring occurs in ~16% of patients and may result in severe airway obstruction.

Pulmonary involvement may be manifested as asymptomatic infiltrates or may be clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort. It is present in 85–90% of patients. Endobronchial disease, either in its active form or as a result of fibrous scarring, may lead to obstruction with atelectasis.

Eye involvement (52% of patients) may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions leading to proptosis.

Skin lesions (46% of patients) appear as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules; biopsy reveals vasculitis, granuloma, or both. Cardiac involvement (8% of patients) manifests as pericarditis, coronary vasculitis, or, rarely, cardiomyopathy. Nervous system manifestations (23% of patients) include cranial neuritis, mononeuritis multiplex, or, rarely, cerebral vasculitis and/or granuloma.

Renal disease (77% of patients) generally dominates the clinical picture and, if left untreated, accounts directly or indirectly for most of the mortality rate in this disease. Although it may smolder in some cases as a mild glomerulitis with proteinuria, hematuria, and red blood cell casts, it is clear that once clinically detectable renal functional impairment occurs, rapidly progressive renal failure usually ensues unless appropriate treatment is instituted.

While the disease is active, most patients have nonspecific symptoms and signs such as malaise, weakness, arthralgias, anorexia, and weight loss. Fever may indicate activity of the underlying disease but more often reflects secondary infection, usually of the upper airway.

Characteristic laboratory findings include a markedly elevated erythrocyte sedimentation rate (ESR), mild anemia and leukocytosis, mild hypergammaglobulinemia (particularly of the IgA class), and mildly elevated rheumatoid factor. Thrombocytosis may be seen as an acute-phase reactant. Approximately 90% of patients with active granulomatosis with polyangiitis (Wegener's) have a positive antiproteinase-3 ANCA. However, in the absence of active disease, the sensitivity drops to ~60–70%. A small percentage of patients with granulomatosis with polyangiitis (Wegener's) may

TABLE 11-5

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S): FREQUENCY OF CLINICAL MANIFESTATIONS IN 158 PATIENTS STUDIED AT THE NATIONAL INSTITUTES OF HEALTH

MANIFESTATION	PERCENT AT DISEASE ONSET	PERCENT THROUGHOUT COURSE OF DISEASE
Kidney		
Glomerulonephritis	18	77
Ear/nose/throat	73	92
Sinusitis	51	85
Nasal disease	36	68
Otitis media	25	44
Hearing loss	14	42
Subglottic stenosis	1	16
Ear pain	9	14
Oral lesions	3	10
Lung	45	85
Pulmonary infiltrates	25	66
Pulmonary nodules	24	58
Hemoptysis	12	30
Pleuritis	10	28
Eyes		
Conjunctivitis	5	18
Dacryocystitis	1	18
Scleritis	6	16
Proptosis	2	15
Eye pain	3	11
Visual loss	0	8
Retinal lesions	0	4
Corneal lesions	0	1
Iritis	0	2
Other[a]		
Arthralgias/arthritis	32	67
Fever	23	50
Cough	19	46
Skin abnormalities	13	46
Weight loss (>10% body weight)	15	35
Peripheral neuropathy	1	15
Central nervous system disease	1	8
Pericarditis	2	6
Hyperthyroidism	1	3

[a]Fewer than 1% had parotid, pulmonary artery, breast, or lower genitourinary (urethra, cervix, vagina, testicular) involvement.
Source: GS Hoffman, U Specks: Arthritis Rheum 41:1521, 1998,

have antimyeloperoxidase rather than antiproteinase-3 antibodies, and up to 20% may lack ANCA.

Patients with granulomatosis with polyangiitis (Wegener's) have been found to have an increased incidence of venous thrombotic events. Although routine anticoagulation for all patients is not recommended, a heightened awareness for any clinical features suggestive of deep venous thrombosis or pulmonary emboli is warranted.

DIAGNOSIS

The diagnosis of granulomatosis with polyangiitis (Wegener's) is made by the demonstration of necrotizing granulomatous vasculitis on tissue biopsy in a patient with compatible clinical features. Pulmonary tissue offers the highest diagnostic yield, almost invariably revealing granulomatous vasculitis. Biopsy of upper airway tissue usually reveals granulomatous inflammation with necrosis but may not show vasculitis. Renal biopsy can confirm the presence of pauci-immune glomerulonephritis.

The specificity of a positive antiproteinase-3 ANCA for granulomatosis with polyangiitis (Wegener's) is very high, especially if active glomerulonephritis is present. However, the presence of ANCA should be adjunctive and, with rare exceptions, should not substitute for a tissue diagnosis. False-positive ANCA titers have been reported in certain infectious and neoplastic diseases.

In its typical presentation, the clinicopathologic complex of granulomatosis with polyangiitis (Wegener's) usually provides ready differentiation from other disorders. However, if all the typical features are not present at once, it needs to be differentiated from the other vasculitides, antiglomerular basement membrane disease (Goodpasture's syndrome), relapsing polychondritis (Chap. 13), tumors of the upper airway or lung, and infectious diseases such as histoplasmosis, mucocutaneous leishmaniasis, and rhinoscleroma as well as noninfectious granulomatous diseases.

Of particular note is the differentiation from NK/T-cell lymphoma nasal type, previously called *midline granuloma*, and *upper airway neoplasms*, which are part of the spectrum of *midline destructive diseases*. These diseases lead to extreme tissue destruction and mutilation localized to the midline upper airway structures including the sinuses; erosion through the skin of the face commonly occurs, a feature that is extremely rare in granulomatosis with polyangiitis (Wegener's). Although blood vessels may be involved in the intense inflammatory reaction and necrosis, primary vasculitis is not seen. NK/T-cell lymphoma nasal type is part of the spectrum of *angiocentric immunoproliferative lesions* and should be treated as such. Localized lesions have responded to local irradiation with 50 Gy (5000 rad). Upper airway lesions should never be irradiated in granulomatosis with polyangiitis (Wegener's). Cocaine-induced tissue injury can be another important mimic of granulomatosis with polyangiitis (Wegener's) in patients who present with isolated midline destructive disease. ANCA that target human neutrophil elastase can be found in patients with cocaine-induced midline destructive lesions and can confound the differentiation from granulomatosis with polyangiitis (Wegener's).

Granulomatosis with polyangiitis (Wegener's) must also be differentiated from *lymphomatoid granulomatosis*, which is an Epstein-Barr virus–positive B cell proliferation that is associated with an exuberant T cell reaction. Lymphomatoid granulomatosis is characterized by lung, skin, CNS, and kidney involvement in which atypical lymphocytoid and plasmacytoid cells infiltrate nonlymphoid tissue in an angioinvasive manner. In this regard, it clearly differs from granulomatosis with polyangiitis (Wegener's) in that it is not an inflammatory vasculitis in the classic sense but an infiltration of vessels with atypical mononuclear cells; granuloma may be present in involved tissues. Up to 50% of patients may develop a true malignant lymphoma.

TREATMENT Granulomatosis with Polyangiitis (Wegener's)

Prior to the introduction of effective therapy, granulomatosis with polyangiitis (Wegener's) was universally fatal within a few months of diagnosis. Glucocorticoids alone led to some symptomatic improvement, with little effect on the ultimate course of the disease. The development of treatment with cyclophophamide dramatically changed patient outcome such that marked improvement was seen in >90% of patients, complete remission in 75% of patients, and 5-year patient survival was seen in over 80%.

Despite the ability to successfully induce remission, 50–70% of remissions are later associated with one or more relapses. The determination of relapse should be based on objective evidence of disease activity, taking care to rule out other features that may have a similar appearance such as infection, medication toxicity, or chronic disease sequelae. The ANCA titer can be misleading and should not be used to assess disease activity. Many patients who achieve remission continue to have elevated titers for years. Results from a large prospective study found that increases in ANCA were not associated with relapse and that only 43% relapsed within 1 year of an increase in ANCA levels. Thus, a rise in ANCA by itself is not a harbinger of immediate disease relapse and should not lead to reinstitution or increase in immunosuppressive therapy.

Reinduction of remission after relapse is almost always achieved; however, a high percentage of patients

ultimately have some degree of damage from irreversible features of their disease, such as varying degrees of renal insufficiency, hearing loss, tracheal stenosis, saddle nose deformity, and chronically impaired sinus function. Patients who developed irreversible renal failure but who achieved subsequent remission have undergone successful renal transplantation.

Because long-term cyclophosphamide is associated with substantial toxicity, approaches have been developed that seek to minimize the duration of exposure to cyclophosphamide while still taking advantage of its efficacy for severe disease. Treatment of granulomatosis with polyangiitis (Wegener's) is currently viewed as having two phases: *induction*, where active disease is put into remission, followed by *maintenance*. The decision regarding which agents to use for induction and maintenance is based upon disease severity together with individual patient factors that include contraindication, relapse history, and comorbidities.

CYCLOPHOSPHAMIDE INDUCTION FOR SEVERE DISEASE For patients with severe disease, daily cyclophosphamide combined with glucocorticoids has been repeatedly proved to effectively induce remission and prolong survival. At the initiation of therapy, glucocorticoids are usually given as prednisone, 1 mg/kg per day for the first month, followed by gradual tapering on an alternate-day or daily schedule with discontinuation after ~6–9 months. Cyclophosphamide is given in doses of 2 mg/kg per day orally, but as it is renally eliminated, dosage reduction should be considered in patients with renal insufficiency. Some reports have indicated therapeutic success with less frequent and severe toxic side effects using IV cyclophosphamide. In a recent randomized trial, IV cyclophosphamide 15 mg/kg, three infusions given every 2 weeks, then every 3 weeks thereafter, was compared to cyclophosphamide 2 mg/kg daily given for 3 months followed by 1.5 mg/kg daily. Although IV cyclophosphamide was found to have a comparable rate of remission with a lower cumulative cyclophosphamide dose and occurrence of leukopenia, the use of a consolidation phase and an insufficient frequency of blood count monitoring may have negatively influenced the results in those who received daily cyclophosphamide. Of note in this study was that relapse occurred in 19% of those who received IV cyclophosphamide as compared to 9% who received daily oral administration. We continue to strongly favor daily cyclophosphamide with utilization of blood count monitoring every 1–2 weeks (as discussed earlier) and limiting the duration of induction exposure to 3–6 months.

In patients with imminently life-threatening disease, such as rapidly progressive glomerulonephritis or pulmonary hemorrhage requiring mechanical ventilation, a regimen of daily cyclophosphamide and glucocorticoids is the treatment of choice to induce remission. Adjunctive plasmapheresis was found to further improve renal recovery in a study of patients with rapidly progressive glomerulonephritis who had a creatinine of greater than 5.8 mg/dL.

REMISSION MAINTENANCE AFTER CYCLOPHOSPHAMIDE After 3–6 months of induction treatment, cyclophosphamide should be stopped and switched to another agent for remission maintenance. The agents with which there has been the greatest published experience are methotrexate and azathioprine. Methotrexate is administered orally or subcutaneously starting at a dosage of 0.3 mg/kg as a single weekly dose, not to exceed 15 mg/week. If the treatment is well tolerated after 1–2 weeks, the dosage should be increased by 2.5 mg weekly up to a dosage of 20–25 mg/week and maintained at that level. Azathioprine, 2 mg/kg per day, has also proved effective in maintaining remission following induction with daily cyclophosphamide. In a randomized trial comparing methotrexate to azathioprine for remission maintenance, comparable rates of toxicity and relapse were seen. Therefore, the choice of agent is often based on toxicity profile, as methotrexate cannot be given to patients with renal insufficiency or chronic liver disease, as well as on other individual patient factors. In patients who are unable to receive methotrexate or azathioprine or who have relapsed through such treatment, mycophenolate mofetil, 1000 mg twice a day, may also sustain remission following cyclophosphamide induction.

The optimal duration of maintenance therapy is uncertain. In the absence of toxicity, maintenance therapy is usually given for a minimum of 2 years past remission, after which time consideration can be given for tapering over a 6–12 month period until discontinuation. Some patients with significant organ damage or a history of relapse may benefit from longer-term continuation of a maintenance agent.

METHOTREXATE INDUCTION FOR NONSEVERE DISEASE For selected patients whose disease is not immediately life threatening or in those patients who have experienced significant cyclophosphamide toxicity, methotrexate together with glucocorticoids given at the dosages described earlier may be considered as an alternative for induction therapy, which is then continued for maintenance.

RITUXIMAB INDUCTION FOR SEVERE DISEASE Rituximab is a chimeric monoclonal antibody directed against CD20 present on normal and malignant B lymphocytes that became FDA approved for granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis in 2011. In two recent randomized

trials that enrolled ANCA positive patients with severe active granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, rituximab 375 mg/m^2 once a week for 4 weeks in combination with glucocorticoids was found to be as effective as cyclophosphamide with glucocorticoids for inducing disease remission. In the trial which also enrolled patients with relapsing disease, rituximab was found to be statistically superior to cyclophosphamide.

While the data supports that rituximab is effective for remission induction severe active granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, there remain a number of ongoing questions regarding rituximab that must be considered in weighing its use in the individual patient. These include that there are no long-term data regarding relapse risk or long-term safety with rituximab, it is unclear how often rituximab needs to be given, and as all patients in the randomized trials were ANCA positive, its efficacy in ANCA negative patients is unknown. It is also uncertain whether the use of other maintenance agents after rituximab would provide any additional benefit in prolonging remission or increase toxicity as these were not used in either randomized trial.

While rituximab does not have the bladder toxicity or infertility concerns, as can occur with cyclophosphamide, in both of the randomized trials, the rate of adverse events was similar in the rituximab and cyclophosphamide arms. Serious side effects of rituximab include infusion reactions, severe mucocutaneous reactions, and rare reports of progressive multifocal leukoencephalopathy. As rituximab can bring about reactivation of hepatitis B, all patients should undergo hepatitis screening prior to treatment with rituximab.

OTHER BIOLOGIC THERAPIES Etanercept, a dimeric fusion protein containing the 75-kDa TNF receptor bound to human IgG1, was not found to sustain remission when used adjunctively to standard therapy and should not be used in the treatment of granulomatosis with polyangiitis (Wegener's).

TRIMETHOPRIM-SULFAMETHOXAZOLE Although certain reports have indicated that TMP-SMX may be of benefit in the treatment of granulomatosis with polyangiitis (Wegener's) isolated to the sinonasal tissues, it should never be used alone to treat active granulomatosis with polyangiitis (Wegener's) outside of the upper airway such as in patients with renal or pulmonary disease. In a study examining the effect of TMP-SMX on relapse, decreased relapses were shown only with regard to upper airway disease, and no differences in major organ relapses were observed.

ORGAN-SPECIFIC TREATMENT Not all manifestations of granulomatosis with polyangiitis (Wegener's) require or respond to cytotoxic therapy. In managing non-major organ disease, such as that isolated to the sinus, joints, or skin, the risks of treatment should be carefully weighed against the benefits. Treatment with cyclophosphamide is rarely if ever justified for the treatment of isolated sinus disease in granulomatosis with polyangiitis (Wegener's). Although patients with non-major organ disease may be effectively treated without cytotoxic therapy, these individuals must be monitored closely for the development of disease activity affecting the lungs, kidneys, or other major organs. Subglottic tracheal stenosis and endobronchial stenosis are examples of disease manifestations that do not typically respond to systemic immunosuppressive treatment.

MICROSCOPIC POLYANGIITIS

DEFINITION

The term *microscopic polyarteritis* was introduced into the literature by Davson in 1948 in recognition of the presence of glomerulonephritis in patients with PAN. In 1992, the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis adopted the term *microscopic polyangiitis* to connote a necrotizing vasculitis with few or no immune complexes affecting small vessels (capillaries, venules, or arterioles). Glomerulonephritis is very common in microscopic polyangiitis, and pulmonary capillaritis often occurs. The absence of granulomatous inflammation in microscopic polyangiitis is said to differentiate it from granulomatosis with polyangiitis (Wegener's).

INCIDENCE AND PREVALENCE

The incidence of microscopic polyangiitis has not yet been reliably established due to its previous inclusion as part of PAN. The mean age of onset is ~57 years of age, and males are slightly more frequently affected than females.

PATHOLOGY AND PATHOGENESIS

The vasculitis seen in microscopic polyangiitis has a predilection to involve capillaries and venules in addition to small and medium-sized arteries. Immunohistochemical staining reveals a paucity of immunoglobulin deposition in the vascular lesion of microscopic polyangiitis, suggesting that immune-complex formation does not play a role in the pathogenesis of this syndrome. The renal lesion seen in microscopic polyangiitis is identical to that of granulomatosis with polyangiitis (Wegener's). Like granulomatosis with polyangiitis (Wegener's),

microscopic polyangiitis is highly associated with the presence of ANCA, which may play a role in pathogenesis of this syndrome (see earlier).

CLINICAL AND LABORATORY MANIFESTATIONS

Because of its predilection to involve the small vessels, microscopic polyangiitis and granulomatosis with polyangiitis (Wegener's) share similar clinical features. Disease onset may be gradual, with initial symptoms of fever, weight loss, and musculoskeletal pain; however, it is often acute. Glomerulonephritis occurs in at least 79% of patients and can be rapidly progressive, leading to renal failure. Hemoptysis may be the first symptom of alveolar hemorrhage, which occurs in 12% of patients. Other manifestations include mononeuritis multiplex and gastrointestinal tract and cutaneous vasculitis. Upper airway disease and pulmonary nodules are not typically found in microscopic polyangiitis and, if present, suggest granulomatosis with polyangiitis (Wegener's).

Features of inflammation may be seen, including an elevated ESR, anemia, leukocytosis, and thrombocytosis. ANCA are present in 75% of patients with microscopic polyangiitis, with antimyeloperoxidase antibodies being the predominant ANCA associated with this disease.

DIAGNOSIS

The diagnosis is based on histologic evidence of vasculitis or pauci-immune glomerulonephritis in a patient with compatible clinical features of multisystem disease. Although microscopic polyangiitis is strongly ANCA-associated, no studies have as yet established the sensitivity and specificity of ANCA in this disease.

TREATMENT Microscopic Polyangiitis

The 5-year survival rate for patients with treated microscopic polyangiitis is 74%, with disease-related mortality occurring from alveolar hemorrhage or gastrointestinal, cardiac, or renal disease. Studies on treatment have come from trials that have included patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. Currently, the treatment approach for microscopic polyangiitis is the same as is used for granulomatosis with polyangiitis (Wegener's) (see "Granulomatosis With Polyangiitis [Wegener's]" for a detailed description of this therapeutic regimen, and patients with immediately life-threatening disease should be treated with the combination of prednisone and daily cyclophosphamide. Recent studies with rituximab also included ANCA positive patients with microscopic polyangiitis. Disease relapse has been observed in at least 34% of patients. Treatment for such relapses would be similar to that used at the time of initial presentation and based upon site and severity of disease.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME)

DEFINITION

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), also referred to as *allergic angiitis and granulomatosis*, was described in 1951 by Churg and Strauss and is characterized by asthma, peripheral and tissue eosinophilia, extravascular granuloma formation, and vasculitis of multiple organ systems.

INCIDENCE AND PREVALENCE

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is an uncommon disease with an estimated annual incidence of 1–3 per million. The disease can occur at any age with the possible exception of infants. The mean age of onset is 48 years, with a female-to-male ratio of 1.2:1.

PATHOLOGY AND PATHOGENESIS

The necrotizing vasculitis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) involves small and medium-sized muscular arteries, capillaries, veins, and venules. A characteristic histopathologic feature of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is granulomatous reactions that may be present in the tissues or even within the walls of the vessels themselves. These are usually associated with infiltration of the tissues with eosinophils. This process can occur in any organ in the body; lung involvement is predominant, with skin, cardiovascular system, kidney, peripheral nervous system, and gastrointestinal tract also commonly involved. Although the precise pathogenesis of this disease is uncertain, its strong association with asthma and its clinicopathologic manifestations, including eosinophilia, granuloma, and vasculitis, point to aberrant immunologic phenomena.

CLINICAL AND LABORATORY MANIFESTATIONS

Patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) often exhibit nonspecific manifestations such as fever, malaise, anorexia, and weight loss, which are characteristic of a multisystem disease. The pulmonary findings in eosinophilic

granulomatosis with polyangiitis (Churg-Strauss syndrome) clearly dominate the clinical picture with severe asthmatic attacks and the presence of pulmonary infiltrates. Mononeuritis multiplex is the second most common manifestation and occurs in up to 72% of patients. Allergic rhinitis and sinusitis develop in up to 61% of patients and are often observed early in the course of disease. Clinically recognizable heart disease occurs in ~14% of patients and is an important cause of mortality. Skin lesions occur in ~51% of patients and include purpura in addition to cutaneous and subcutaneous nodules. The renal disease in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is less common and generally less severe than that of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis.

The characteristic laboratory finding in virtually all patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is a striking eosinophilia, which reaches levels >1000 cells/μL in >80% of patients. Evidence of inflammation as evidenced by elevated ESR, fibrinogen, or α_2-globulins can be found in 81% of patients. The other laboratory findings reflect the organ systems involved. Approximately 40% of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) have circulating ANCA that is usually antimyeloperoxidase.

DIAGNOSIS

Although the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is optimally made by biopsy in a patient with the characteristic clinical manifestations (see earlier), histologic confirmation can be challenging as the pathognomonic features often do not occur simultaneously. In order to be diagnosed with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), a patient should have evidence of asthma, peripheral blood eosinophilia, and clinical features consistent with vasculitis.

TREATMENT Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

The prognosis of untreated eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) is poor, with a reported 5-year survival of 25%. With treatment, prognosis is favorable, with one study finding a 78-month actuarial survival rate of 72%. Myocardial involvement is the most frequent cause of death and is responsible for 39% of patient mortality. Glucocorticoids alone appear to be effective in many patients. Dosage tapering is often limited by asthma, and many patients require low-dose prednisone for persistent asthma many years after clinical recovery from vasculitis. In glucocorticoid failure or in patients who present with fulminant multisystem disease, the treatment of choice is a combined regimen of daily cyclophosphamide and prednisone see "Granulomatosis With Polyangiitis [Wegener's]" for a detailed description of this therapeutic regimen).

POLYARTERITIS NODOSA

DEFINITION

PAN, also referred to as *classic PAN*, was described in 1866 by Kussmaul and Maier. It is a multisystem, necrotizing vasculitis of small and medium-sized muscular arteries in which involvement of the renal and visceral arteries is characteristic. PAN does not involve pulmonary arteries, although bronchial vessels may be involved; granulomas, significant eosinophilia, and an allergic diathesis are not observed.

INCIDENCE AND PREVALENCE

It is difficult to establish an accurate incidence of PAN because previous reports have included PAN and microscopic polyangiitis as well as other related vasculitides. PAN, as currently defined, is felt to be a very uncommon disease.

PATHOLOGY AND PATHOGENESIS

The vascular lesion in PAN is a necrotizing inflammation of small and medium-sized muscular arteries. The lesions are segmental and tend to involve bifurcations and branchings of arteries. They may spread circumferentially to involve adjacent veins. However, involvement of venules is not seen in PAN and, if present, suggests microscopic polyangiitis (see next). In the acute stages of disease, polymorphonuclear neutrophils infiltrate all layers of the vessel wall and perivascular areas, which results in intimal proliferation and degeneration of the vessel wall. Mononuclear cells infiltrate the area as the lesions progress to the subacute and chronic stages. Fibrinoid necrosis of the vessels ensues with compromise of the lumen, thrombosis, infarction of the tissues supplied by the involved vessel, and, in some cases, hemorrhage. As the lesions heal, there is collagen deposition, which may lead to further occlusion of the vessel lumen. Aneurysmal dilations up to 1 cm in size along the involved arteries are characteristic of PAN. Granulomas and substantial eosinophilia with eosinophilic tissue infiltrations are not characteristically found and suggest eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (see earlier).

Multiple organ systems are involved, and the clinicopathologic findings reflect the degree and location of vessel involvement and the resulting ischemic changes. As mentioned earlier, pulmonary arteries are not involved in PAN, and bronchial artery involvement is uncommon. The pathology in the kidney in classic PAN is that of arteritis without glomerulonephritis. In patients with significant hypertension, typical pathologic features of glomerulosclerosis may be seen. In addition, pathologic sequelae of hypertension may be found elsewhere in the body.

The presence of a PAN-like vasculitis in patients with hepatitis B together with the isolation of circulating immune complexes composed of hepatitis B antigen and immunoglobulin, and the demonstration by immunofluorescence of hepatitis B antigen, IgM, and complement in the blood vessel walls, strongly suggest the role of immunologic phenomena in the pathogenesis of this disease. Hairy cell leukemia can be associated with PAN; the pathogenic mechanisms of this association are unclear.

CLINICAL AND LABORATORY MANIFESTATIONS

Nonspecific signs and symptoms are the hallmarks of PAN. Fever, weight loss, and malaise are present in over one-half of cases. Patients usually present with vague symptoms such as weakness, malaise, headache, abdominal pain, and myalgias that can rapidly progress to a fulminant illness. Specific complaints related to the vascular involvement within a particular organ system may also dominate the presenting clinical picture as well as the entire course of the illness **(Table 11-6)**. In PAN, renal involvement most commonly manifests as hypertension, renal insufficiency, or hemorrhage due to microaneurysms.

There are no diagnostic serologic tests for PAN. In >75% of patients, the leukocyte count is elevated with a predominance of neutrophils. Eosinophilia is seen only rarely and, when present at high levels, suggests the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). The anemia of chronic disease may be seen, and an elevated ESR is almost always present. Other common laboratory findings reflect the particular organ involved. Hypergammaglobulinemia may be present, and all patients should be screened for hepatitis B. Antibodies against myeloperoxidase or proteinase-3 (ANCA) are rarely found in patients with PAN.

DIAGNOSIS

The diagnosis of PAN is based on the demonstration of characteristic findings of vasculitis on biopsy material of involved organs. In the absence of easily accessible tissue for biopsy, the arteriographic demonstration of involved vessels, particularly in the form of aneurysms of small and medium-sized arteries in the renal, hepatic, and visceral vasculature, is sufficient to make the diagnosis. Aneurysms of vessels are not pathognomonic of PAN; furthermore, aneurysms need not always be present, and arteriographic findings may be limited to stenotic segments and obliteration of vessels. Biopsy of symptomatic organs such as nodular skin lesions, painful testes, and nerve/muscle provides the highest diagnostic yields.

TABLE 11-6

CLINICAL MANIFESTATIONS RELATED TO ORGAN SYSTEM INVOLVEMENT IN CLASSIC POLYARTERITIS NODOSA

ORGAN SYSTEM	PERCENT INCIDENCE	CLINICAL MANIFESTATIONS
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud's phenomenon
Cardiac	36	Congestive heart failure, myocar-dial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

Source: From TR Cupps, AS Fauci: *The Vasculitides*. Philadelphia, Saunders, 1981.

TREATMENT **Polyarteritis Nodosa**

The prognosis of untreated PAN is extremely poor, with a reported 5-year survival rate between 10 and 20%. Death usually results from gastrointestinal complications, particularly bowel infarcts and perforation, and cardiovascular causes. Intractable hypertension often compounds dysfunction in other organ systems, such as the kidneys, heart, and CNS, leading to additional late morbidity and mortality in PAN. With the introduction

of treatment, survival rate has increased substantially. Favorable therapeutic results have been reported in PAN with the combination of prednisone and cyclophosphamide (see "Granulomatosis With Polyangiitis [Wegener's]" for a detailed description of this therapeutic regimen). In less severe cases of PAN, glucocorticoids alone have resulted in disease remission. In patients with hepatitis B who have a PAN-like vasculitis, antiviral therapy represents an important part of therapy and has been used in combination with glucocorticoids and plasma exchange. Careful attention to the treatment of hypertension can lessen the acute and late morbidity and mortality rates associated with renal, cardiac, and CNS complications of PAN. Following successful treatment, relapse of PAN has been estimated to occur in 10–20% of patients.

GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA

DEFINITION

Giant cell arteritis, also referred to as *cranial arteritis* or *temporal arteritis*, is an inflammation of medium- and large-sized arteries. It characteristically involves one or more branches of the carotid artery, particularly the temporal artery. However, it is a systemic disease that can involve arteries in multiple locations, particularly the aorta and its main branches.

Giant cell arteritis is closely associated with *polymyalgia rheumatica*, which is characterized by stiffness, aching, and pain in the muscles of the neck, shoulders, lower back, hips, and thighs. Most commonly, polymyalgia rheumatica occurs in isolation, but it may be seen in 40–50% of patients with giant cell arteritis. In addition, ~10–20% of patients who initially present with features of isolated polymyalgia rheumatica later go on to develop giant cell arteritis. This strong clinical association together with data from pathophysiologic studies has increasingly supported that giant cell arteritis and polymyalgia rheumatica represent differing clinical spectrums of a single disease process.

INCIDENCE AND PREVALENCE

Giant cell arteritis occurs almost exclusively in individuals >50 years. It is more common in women than in men and is rare in blacks. The incidence of giant cell arteritis varies widely in different studies and in different geographic regions. A high incidence has been found in Scandinavia and in regions of the United States with large Scandinavian populations, compared to a lower incidence in southern Europe. The annual incidence rates in individuals ≥50 years range from 6.9 to 32.8 per 100,000 population. Familial aggregation has been reported, as has an association with HLA-DR4. In addition, genetic linkage studies have demonstrated an association of giant cell arteritis with alleles at the HLA-DRB1 locus, particularly HLA-DRB1* 04 variants. In Olmsted County, Minnesota, the annual incidence of polymyalgia rheumatica in individuals ≥50 years is 58.7 per 100,000 population.

PATHOLOGY AND PATHOGENESIS

Although the temporal artery is most frequently involved in giant cell arteritis, patients often have a systemic vasculitis of multiple medium- and large-sized arteries, which may go undetected. Histopathologically, the disease is a panarteritis with inflammatory mononuclear cell infiltrates within the vessel wall with frequent giant cell formation. There is proliferation of the intima and fragmentation of the internal elastic lamina. Pathophysiologic findings in organs result from the ischemia related to the involved vessels.

Experimental data support that giant cell arteritis is an antigen-driven disease in which activated T lymphocytes, macrophages, and dendritic cells play a critical role in the disease pathogenesis. Sequence analysis of the T cell receptor of tissue-infiltrating T cells in lesions of giant cell arteritis indicates restricted clonal expansion, suggesting the presence of an antigen residing in the arterial wall. Giant cell arteritis is believed to be initiated in the adventitia where CD4+ T cells enter through the vasa vasorum, become activated, and orchestrate macrophage differentiation. T cells recruited to vasculitic lesions in patients with giant cell arteritis produce predominantly IL-2 and IFN-γ, and the latter has been suggested to be involved in the progression to overt arteritis.

CLINICAL AND LABORATORY MANIFESTATIONS

Giant cell arteritis is most commonly characterized clinically by the complex of fever, anemia, high ESR, and headaches in a patient over the age of 50 years. Other phenotypic manifestations include features of systemic inflammation including malaise, fatigue, anorexia, weight loss, sweats, arthralgias, polymyalgia rheumatica, or large-vessel disease.

In patients with involvement of the cranial arteries, headache is the predominant symptom and may be associated with a tender, thickened, or nodular artery, which may pulsate early in the disease but may become occluded later. Scalp pain and claudication of the jaw and tongue may occur. A well-recognized and dreaded complication of giant cell arteritis, particularly in untreated patients, is ischemic optic neuropathy, which may lead to serious visual symptoms, even sudden

blindness in some patients. However, most patients have complaints relating to the head or eyes before visual loss. Attention to such symptoms with institution of appropriate therapy (see later in chapter) will usually avoid this complication. Other cranial ischemic complications include strokes, scalp or tongue infarction.

Up to one-third of patients can have large-vessel disease that can be the primary presentation of giant cell arteritis or can emerge at a later point in patients who have had previous cranial arteritis features or polymyalgia rheumatica. Manifestations of large-vessel disease can include subclavian artery stenosis that can present as arm claudication or aortic aneurysms involving the thoracic and to a lesser degree the abdominal aorta, which carry risks of rupture or dissection.

Characteristic laboratory findings in addition to the elevated ESR include a normochromic or slightly hypochromic anemia. Liver function abnormalities are common, particularly increased alkaline phosphatase levels. Increased levels of IgG and complement have been reported. Levels of enzymes indicative of muscle damage such as serum creatine kinase are not elevated.

DIAGNOSIS

The diagnosis of giant cell arteritis and its associated clinicopathologic syndrome can often be suggested clinically by the demonstration of the complex of fever, anemia, and high ESR with or without symptoms of polymyalgia rheumatica in a patient >50 years. The diagnosis is confirmed by biopsy of the temporal artery. Since involvement of the vessel may be segmental, positive yield is increased by obtaining a biopsy segment of 3–5 cm together with serial sectioning of biopsy specimens. Ultrasonography of the temporal artery has been reported to be helpful in diagnosis. A temporal artery biopsy should be obtained as quickly as possible in the setting of ocular signs and symptoms, and under these circumstances therapy should not be delayed pending a biopsy. In this regard, it has been reported that temporal artery biopsies may show vasculitis even after ~14 days of glucocorticoid therapy. A dramatic clinical response to a trial of glucocorticoid therapy can further support the diagnosis.

Large vessel disease may be suggested by symptoms and findings on physical examination such as diminished pulses or bruits. It is confirmed by vascular imaging, most commonly through magnetic resonance or computed tomography.

Isolated polymyalgia rheumatica is a clinical diagnosis made by the presence of typical symptoms of stiffness, aching, and pain in the muscles of the hip and shoulder girdle, an increased ESR, the absence of clinical features suggestive of giant cell arteritis, and a prompt therapeutic response to low-dose prednisone.

TREATMENT Giant Cell Arteritis and Polymyalgia Rheumatica

Acute disease-related mortality directly from giant cell arteritis is very uncommon with fatalities occurring from cerebrovascular events or myocardial infarction. However, patients are at risk of late mortality from aortic aneurysm rupture or dissection as patients with giant cell arteritis are 18 times more likely to develop thoracic aortic aneurysms than the general population.

The goals of treatment in giant cell arteritis are to reduce symptoms and, most importantly, to prevent visual loss. The treatment approach for cranial and large-vessel disease in giant cell arteritis is currently the same. Giant cell arteritis and its associated symptoms are exquisitely sensitive to glucocorticoid therapy. Treatment should begin with prednisone, 40–60 mg/d for ~1 month, followed by a gradual tapering. When ocular signs and symptoms occur, consideration should be given for the use of methylprednisolone 1000 mg daily for 3 days to protect remaining vision. Although the optimal duration of glucocorticoid therapy has not been established, most series have found that patients require treatment for ≥2 years. Symptom recurrence during prednisone tapering develops in 60–85% of patients with giant cell arteritis, requiring a dosage increase. The ESR can serve as a useful indicator of inflammatory disease activity in monitoring and tapering therapy and can be used to judge the pace of the tapering schedule. However, minor increases in the ESR can occur as glucocorticoids are being tapered and do not necessarily reflect an exacerbation of arteritis, particularly if the patient remains symptom-free. Under these circumstances, the tapering should continue with caution. Glucocorticoid toxicity occurs in 35–65% of patients and represents an important cause of patient morbidity. Aspirin 81 mg daily has been found to reduce the occurrence of cranial ischemic complications in giant cell arteritis and should be given in addition to glucocorticoids in patients who do not have contraindications. The use of weekly methotrexate as a glucocorticoid-sparing agent has been examined in two randomized placebo-controlled trials that reached conflicting conclusions. Infliximab, a monoclonal antibody to TNF, was studied in a randomized trial and was not found to provide benefit.

Patients with isolated polymyalgia rheumatica respond promptly to prednisone, which can be started at a lower dose of 10–20 mg/d. Similar to giant cell arteritis, the ESR can serve as a useful indicator in monitoring and prednisone reduction. Recurrent polymyalgia symptoms develop in the majority of patients during prednisone tapering. One study of weekly methotrexate found that the use of this drug reduced the prednisone dose on average by only 1 mg and did not decrease

prednisone-related side effects. A randomized trial in polymyalgia rheumatica did not find infliximab to lessen relapse or glucocorticoid requirements.

TAKAYASU ARTERITIS

DEFINITION

Takayasu arteritis is an inflammatory and stenotic disease of medium- and large-sized arteries characterized by a strong predilection for the aortic arch and its branches. For this reason, it is often referred to as the *aortic arch syndrome*.

INCIDENCE AND PREVALENCE

Takayasu arteritis is an uncommon disease with an estimated annual incidence rate of 1.2–2.6 cases per million. It is most prevalent in adolescent girls and young women. Although it is more common in Asia, it is neither racially nor geographically restricted.

PATHOLOGY AND PATHOGENESIS

The disease involves medium- and large-sized arteries, with a strong predilection for the aortic arch and its branches; the pulmonary artery may also be involved. The most commonly affected arteries seen by arteriography are listed in **Table 11-7**. The involvement of the major branches of the aorta is much more marked at their origin than distally. The disease is a panarteritis with inflammatory mononuclear cell infiltrates and occasionally giant cells. There are marked intimal proliferation and fibrosis, scarring and vascularization of the media, and disruption and degeneration of the elastic lamina. Narrowing of the lumen occurs with or without thrombosis. The vasa vasorum are frequently involved. Pathologic changes in various organs reflect the compromise of blood flow through the involved vessels.

Immunopathogenic mechanisms, the precise nature of which is uncertain, are suspected in this disease. As with several of the vasculitis syndromes, circulating immune complexes have been demonstrated, but their pathogenic significance is unclear.

CLINICAL AND LABORATORY MANIFESTATIONS

Takayasu arteritis is a systemic disease with generalized as well as vascular symptoms. The generalized symptoms include malaise, fever, night sweats, arthralgias, anorexia, and weight loss, which may occur months before vessel involvement is apparent. These symptoms may merge into those related to vascular compromise and organ ischemia. Pulses are commonly absent in the involved vessels, particularly the subclavian artery. The frequency of arteriographic abnormalities and the potentially associated clinical manifestations are listed in Table 11-7. Hypertension occurs in 32–93% of patients and contributes to renal, cardiac, and cerebral injury.

Characteristic laboratory findings include an elevated ESR, mild anemia, and elevated immunoglobulin levels.

TABLE 11-7
FREQUENCY OF ARTERIOGRAPHIC ABNORMALITIES AND POTENTIAL CLINICAL MANIFESTATIONS OF ARTERIAL INVOLVEMENT IN TAKAYASU ARTERITIS

ARTERY	PERCENT OF ARTERIOGRAPHIC ABNORMALITIES	POTENTIAL CLINICAL MANIFESTATIONS
Subclavian	93	Arm claudication, Raynaud's phenomenon
Common carotid	58	Visual changes, syncope, transient ischemic attacks, stroke
Abdominal aorta[a]	47	Abdominal pain, nausea, vomiting
Renal	38	Hypertension, renal failure
Aortic arch or root	35	Aortic insufficiency, congestive heart failure
Vertebral	35	Visual changes, dizziness
Coeliac axis[a]	18	Abdominal pain, nausea, vomiting
Superior mesenteric[a]	18	Abdominal pain, nausea, vomiting
Iliac	17	Leg claudication
Pulmonary	10–40	Atypical chest pain, dyspnea
Coronary	<10	Chest pain, myocardial infarction

[a]Arteriographic lesions at these locations are usually asymptomatic but may potentially cause these symptoms.
Source: G Kerr et al: Ann Intern Med 120:919, 1994.

DIAGNOSIS

The diagnosis of Takayasu arteritis should be suspected strongly in a young woman who develops a decrease or absence of peripheral pulses, discrepancies in blood pressure, and arterial bruits. The diagnosis is confirmed by the characteristic pattern on arteriography, which includes irregular vessel walls, stenosis, poststenotic

dilation, aneurysm formation, occlusion, and evidence of increased collateral circulation. Complete aortic arteriography by catheter-directed dye arteriography or magnetic resonance arteriography should be obtained in order to fully delineate the distribution and degree of arterial disease. Histopathologic demonstration of inflamed vessels adds confirmatory data; however, tissue is rarely readily available for examination.

TREATMENT Takayasu Arteritis

The long-term outcome of patients with Takayasu arteritis has varied widely between studies. Although two North American reports found overall survival to be >94%, the 5-year mortality rate from other studies has ranged from 0 to 35%. Disease-related mortality most often occurs from congestive heart failure, cerebrovascular events, myocardial infarction, aneurysm rupture, or renal failure. Even in the absence of life-threatening disease, Takayasu arteritis can be associated with significant morbidity. The course of the disease is variable, and although spontaneous remissions may occur, Takayasu arteritis is most often chronic and relapsing. Although glucocorticoid therapy in doses of 40–60 mg prednisone per day alleviates symptoms, there are no convincing studies that indicate that they increase survival. The combination of glucocorticoid therapy for acute signs and symptoms and an aggressive surgical and/or arterioplastic approach to stenosed vessels has markedly improved outcome and decreased morbidity by lessening the risk of stroke, correcting hypertension due to renal artery stenosis, and improving blood flow to ischemic viscera and limbs. Unless it is urgently required, surgical correction of stenosed arteries should be undertaken only when the vascular inflammatory process is well controlled with medical therapy. In individuals who are refractory to or unable to taper glucocorticoids, methotrexate in doses up to 25 mg per week has yielded encouraging results. Preliminary results with anti-TNF therapies have been encouraging, but will require further study through randomized trials to determine efficacy.

IGA VASCULITIS (HENOCH-SCHÖNLEIN)

DEFINITION

IgA vasculitis (Henoch-Schönlein), also referred to as *Henoch-Schönlein purpura* or *anaphylactoid purpura*, is a small-vessel vasculitis characterized by palpable purpura (most commonly distributed over the buttocks and lower extremities), arthralgias, gastrointestinal signs and symptoms, and glomerulonephritis.

INCIDENCE AND PREVALENCE

IgA vasculitis (Henoch-Schönlein) is usually seen in children; most patients range in age from 4 to 7 years; however, the disease may also be seen in infants and adults. It is not a rare disease; in one series it accounted for between 5 and 24 admissions per year at a pediatric hospital. The male-to-female ratio is 1.5:1. A seasonal variation with a peak incidence in spring has been noted.

PATHOLOGY AND PATHOGENESIS

The presumptive pathogenic mechanism for IgA vasculitis (Henoch-Schönlein) is immune-complex deposition. A number of inciting antigens have been suggested including upper respiratory tract infections, various drugs, foods, insect bites, and immunizations. IgA is the antibody class most often seen in the immune complexes and has been demonstrated in the renal biopsies of these patients.

CLINICAL AND LABORATORY MANIFESTATIONS

In pediatric patients, palpable purpura is seen in virtually all patients; most patients develop polyarthralgias in the absence of frank arthritis. Gastrointestinal involvement, which is seen in almost 70% of pediatric patients, is characterized by colicky abdominal pain usually associated with nausea, vomiting, diarrhea, or constipation and is frequently accompanied by the passage of blood and mucus per rectum; bowel intussusception may occur. Renal involvement occurs in 10–50% of patients and is usually characterized by mild glomerulonephritis leading to proteinuria and microscopic hematuria, with red blood cell casts in the majority of patients; it usually resolves spontaneously without therapy. Rarely, a progressive glomerulonephritis will develop. In adults, presenting symptoms are most frequently related to the skin and joints, while initial complaints related to the gut are less common. Although certain studies have found that renal disease is more frequent and more severe in adults, this has not been a consistent finding. However, the course of renal disease in adults may be more insidious and thus requires close follow-up. Myocardial involvement can occur in adults but is rare in children.

Laboratory studies generally show a mild leukocytosis, a normal platelet count, and occasionally eosinophilia. Serum complement components are normal, and IgA levels are elevated in about one-half of patients.

DIAGNOSIS

The diagnosis of IgA vasculitis (Henoch-Schonlein) is based on clinical signs and symptoms. Skin biopsy specimen can be useful in confirming leukocytoclastic

vasculitis with IgA and C3 deposition by immunofluorescence. Renal biopsy is rarely needed for diagnosis but may provide prognostic information in some patients.

TREATMENT **IgA Vasculitis (Henoch-Schönlein)**

The prognosis of IgA vasculitis (Henoch-Schönlein) is excellent. Mortality is exceedingly rare, and 1–5% of children progress to end-stage renal disease. Most patients recover completely, and some do not require therapy. Treatment is similar for adults and children. When glucocorticoid therapy is required, prednisone, in doses of 1 mg/kg per day and tapered according to clinical response, has been shown to be useful in decreasing tissue edema, arthralgias, and abdominal discomfort; however, it has not proved beneficial in the treatment of skin or renal disease and does not appear to shorten the duration of active disease or lessen the chance of recurrence. Patients with rapidly progressive glomerulonephritis have been anecdotally reported to benefit from intensive plasma exchange combined with cytotoxic drugs. Disease recurrences have been reported in 10–40% of patients.

IDIOPATHIC CUTANEOUS VASCULITIS

DEFINITION

The term *cutaneous vasculitis* is defined broadly as inflammation of the blood vessels of the dermis. Due to its heterogeneity, cutaneous vasculitis has been described by a variety of terms including *hypersensitivity vasculitis* and *cutaneous leukocytoclastic angiitis*. However, cutaneous vasculitis is not one specific disease but a manifestation that can be seen in a variety of settings. In >70% of cases, cutaneous vasculitis occurs either as part of a primary systemic vasculitis or as a secondary vasculitis related to an inciting agent or an underlying disease (see "Secondary Vasculitis," later in chapter). In the remaining 30% of cases, cutaneous vasculitis occurs idiopathically.

INCIDENCE AND PREVALENCE

Cutaneous vasculitis represents the most commonly encountered vasculitis in clinical practice. The exact incidence of idiopathic cutaneous vasculitis has not been determined due to the predilection for cutaneous vasculitis to be associated with an underlying process and the variability of its clinical course.

PATHOLOGY AND PATHOGENESIS

The typical histopathologic feature of cutaneous vasculitis is the presence of vasculitis of small vessels. Postcapillary venules are the most commonly involved vessels; capillaries and arterioles may be involved less frequently. This vasculitis is characterized by a *leukocytoclasis*, a term that refers to the nuclear debris remaining from the neutrophils that have infiltrated in and around the vessels during the acute stages. In the subacute or chronic stages, mononuclear cells predominate; in certain subgroups, eosinophilic infiltration is seen. Erythrocytes often extravasate from the involved vessels, leading to palpable purpura.

CLINICAL AND LABORATORY MANIFESTATIONS

The hallmark of idiopathic cutaneous vasculitis is the predominance of skin involvement. Skin lesions may appear typically as palpable purpura; however, other cutaneous manifestations of the vasculitis may occur, including macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. The skin lesions may be pruritic or even quite painful, with a burning or stinging sensation. Lesions most commonly occur in the lower extremities in ambulatory patients or in the sacral area in bedridden patients due to the effects of hydrostatic forces on the postcapillary venules. Edema may accompany certain lesions, and hyperpigmentation often occurs in areas of recurrent or chronic lesions.

There are no specific laboratory tests diagnostic of idiopathic cutaneous vasculitis. A mild leukocytosis with or without eosinophilia is characteristic, as is an elevated ESR. Laboratory studies should be aimed toward ruling out features to suggest an underlying disease or a systemic vasculitis.

DIAGNOSIS

The diagnosis of cutaneous vasculitis is made by the demonstration of vasculitis on biopsy. An important diagnostic principle in patients with cutaneous vasculitis is to search for an etiology of the vasculitis—be it an exogenous agent, such as a drug or an infection, or an endogenous condition, such as an underlying disease (Fig. 11-1). In addition, a careful physical and laboratory examination should be performed to rule out the possibility of systemic vasculitis. This should start with the least invasive diagnostic approach and proceed to the more invasive only if clinically indicated.

TREATMENT **Idiopathic Cutaneous Vasculitis**

When an antigenic stimulus is recognized as the precipitating factor in the cutaneous vasculitis, it should be removed; if this is a microbe, appropriate

antimicrobial therapy should be instituted. If the vasculitis is associated with another underlying disease, treatment of the latter often results in resolution of the former. In situations where disease is apparently self-limited, no therapy, except possibly symptomatic therapy, is indicated. When cutaneous vasculitis persists and when there is no evidence of an inciting agent, an associated disease, or an underlying systemic vasculitis, the decision to treat should be based on weighing the balance between the degree of symptoms and the risk of treatment. Some cases of idiopathic cutaneous vasculitis resolve spontaneously, while others remit and relapse. In those patients with persistent vasculitis, a variety of therapeutic regimens have been tried with variable results. In general, the treatment of idiopathic cutaneous vasculitis has not been satisfactory. Fortunately, since the disease is generally limited to the skin, this lack of consistent response to therapy usually does not lead to a life-threatening situation. Agents with which there have been anecdotal reports of success include dapsone, colchicine, hydroxychloroquine, and nonsteroidal anti-inflammatory agents. Glucocorticoids are often used in the treatment of idiopathic cutaneous vasculitis. Therapy is usually instituted as prednisone, 1 mg/kg per day, with rapid tapering where possible, either directly to discontinuation or by conversion to an alternate-day regimen followed by ultimate discontinuation. In cases that prove refractory to glucocorticoids, a trial of a cytotoxic agent may be indicated. Patients with chronic vasculitis isolated to cutaneous venules rarely respond dramatically to any therapeutic regimen, and cytotoxic agents should be used only as a last resort in these patients. Methotrexate and azathioprine have been used in such situations in anecdotal reports. Although cyclophosphamide is a very effective therapy for the systemic vasculitides, it should almost never be used for idiopathic cutaneous vasculitis because of the potential toxicity.

CRYOGLOBULINEMIC VASCULITIS

DEFINITION

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins. Cryoglobulinemia may be associated with a systemic vasculitis characterized by palpable purpura, arthralgias, weakness, neuropathy, and glomerulonephritis. Although this can be observed in association with a variety of underlying disorders including multiple myeloma, lymphoproliferative disorders, connective tissue diseases, infection, and liver disease, in many instances it appeared to be idiopathic. Because of the apparent absence of an underlying disease and the presence of cryoprecipitate containing oligoclonal/polyclonal immunoglobulins, this entity was referred to as *essential mixed cryoglobulinemia*. Since the discovery of hepatitis C, it has been established that the vast majority of patients who were considered to have essential mixed cryoglobulinemia have cryoglobulinemic vasculitis related to hepatitis C infection.

INCIDENCE AND PREVALENCE

The incidence of cryoglobulinemic vasculitis has not been established. It has been estimated, however, that 5% of patients with chronic hepatitis C will develop cryoglobulinemic vasculitis.

PATHOLOGY AND PATHOGENESIS

Skin biopsies in cryoglobulinemic vasculitis reveal an inflammatory infiltrate surrounding and involving blood vessel walls, with fibrinoid necrosis, endothelial cell hyperplasia, and hemorrhage. Deposition of immunoglobulin and complement is common. Abnormalities of uninvolved skin including basement membrane alterations and deposits in vessel walls may be found. Membranoproliferative glomerulonephritis is responsible for 80% of all renal lesions in cryoglobulinemic vasculitis.

The association between hepatitis C and cryoglobulinemic vasculitis has been supported by the high frequency of documented hepatitis C infection, the presence of hepatitis C RNA and anti–hepatitis C antibodies in serum cryoprecipitates, evidence of hepatitis C antigens in vasculitic skin lesions, and the effectiveness of antiviral therapy (see next). Current evidence suggests that in the majority of cases, cryoglobulinemic vasculitis occurs when an aberrant immune response to hepatitis C infection leads to the formation of immune complexes consisting of hepatitis C antigens, polyclonal hepatitis C–specific IgG, and monoclonal IgM rheumatoid factor. The deposition of these immune complexes in blood vessel walls triggers an inflammatory cascade that results in cryoglobulinemic vasculitis.

CLINICAL AND LABORATORY MANIFESTATIONS

The most common clinical manifestations of cryoglobulinemic vasculitis are cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis. Renal disease develops in 10–30% of patients. Life-threatening rapidly progressive glomerulonephritis or vasculitis of the CNS, gastrointestinal tract, or heart occurs infrequently.

The presence of circulating cryoprecipitates is the fundamental finding in cryoglobulinemic vasculitis. Rheumatoid factor is almost always found and may be a useful clue to the disease when cryoglobulins are not detected. Hypocomplementemia occurs in 90% of

patients. An elevated ESR and anemia occur frequently. Evidence for hepatitis C infection must be sought in all patients by testing for hepatitis C antibodies and hepatitis C RNA.

TREATMENT **Cryoglobulinemic Vasculitis**

Acute mortality directly from cryoglobulinemic vasculitis is uncommon, but the presence of glomerulonephritis is a poor prognostic sign for overall outcome. In such patients, 15% progress to end-stage renal disease, with 40% later experiencing fatal cardiovascular disease, infection, or liver failure. As indicated earlier, the majority of cases are associated with hepatitis C infection. In such patients, treatment with pegylated IFN and ribavirin can prove beneficial. Clinical improvement with antiviral therapy is dependent on the virologic response. Patients who clear hepatitis C from the blood have objective improvement in their vasculitis along with significant reductions in levels of circulating cryoglobulins, IgM, and rheumatoid factor. However, substantial portions of patients with hepatitis C do not have a sustained virologic response to such therapy, and the vasculitis typically relapses with the return of viremia. While transient improvement can be observed with glucocorticoids, a complete response is seen in only 7% of patients. Plasmapheresis and cytotoxic agents have been used in anecdotal reports. These observations have not been confirmed, and such therapies carry significant risks. Recent studies have found rituximab (anti-CD20) to be effective in hepatitis C associated cryoglobulinemic vasculitis, particularly in patients who have been resistant to or intolerant of anti-viral therapy.

BEHÇET'S DISEASE

Behçet's disease is a clinicopathologic entity characterized by recurrent episodes of oral and genital ulcers, iritis, and cutaneous lesions. The underlying pathologic process is a leukocytoclastic venulitis, although vessels of any size and in any organ can be involved. This disorder is described in detail in Chap. 12.

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

Primary central nervous system vasculitis, which is also called *isolated vasculitis of the central nervous system* or (PACNS), is an uncommon clinicopathologic entity characterized by vasculitis restricted to the vessels of the CNS without other apparent systemic vasculitis. The inflammatory process is usually composed of mononuclear cell infiltrates with or without granuloma formation.

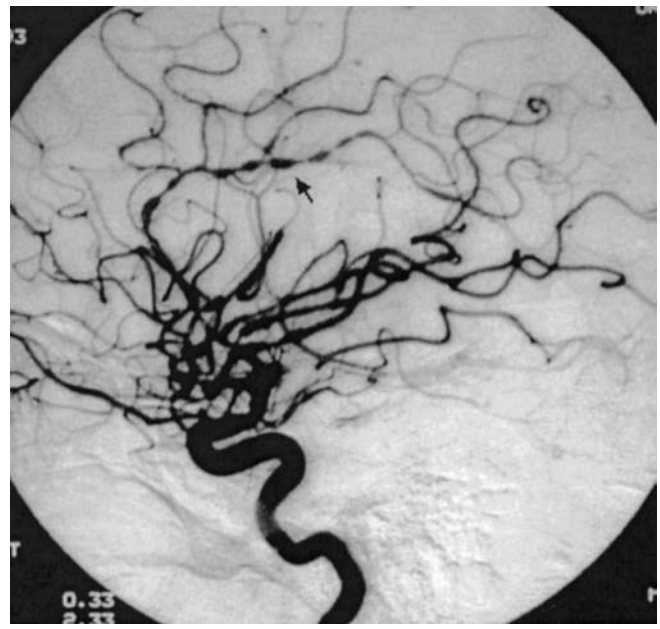


FIGURE 11-4
Cerebral arteriogram from a 32-year-old male with central nervous system vasculitis. Dramatic beading (*arrow*) typical of vasculitis is seen.

Patients may present with headaches, altered mental function, and focal neurologic defects. Systemic symptoms are generally absent. Devastating neurologic abnormalities may occur depending on the extent of vessel involvement. The diagnosis can be suggested by abnormal MRI of the brain, an abnormal lumbar puncture, and/or demonstration of characteristic vessel abnormalities on arteriography **(Fig. 11-4)**, but it is confirmed by biopsy of the brain parenchyma and leptomeninges. In the absence of a brain biopsy, care should be taken not to misinterpret as true primary vasculitis arteriographic abnormalities that might actually be related to another cause. An important entity in the differential diagnosis is reversible cerebral vasoconstrictive syndrome, which typically presents with "thunderclap" headache and is associated with arteriographic abnormalities that mimic PACNS that are reversible. Other diagnostic considerations include infection, atherosclerosis, emboli, connective tissue disease, sarcoidosis, malignancy, and drug-associated causes. The prognosis of granulomatous PACNS is poor; however, some reports indicate that glucocorticoid therapy, alone or together with cyclophosphamide administered as described earlier, has induced clinical remissions.

COGAN'S SYNDROME

Cogan's syndrome is characterized by interstitial keratitis together with vestibuloauditory symptoms. It may be

associated with a systemic vasculitis, particularly aortitis with involvement of the aortic valve. Glucocorticoids are the mainstay of treatment. Initiation of treatment as early as possible after the onset of hearing loss improves the likelihood of a favorable outcome.

KAWASAKI DISEASE

Kawasaki disease, also referred to as *mucocutaneous lymph node syndrome*, is an acute, febrile, multisystem disease of children. Some 80% of cases occur prior to the age of 5, with the peak incidence occurring at ≤2 years. It is characterized by nonsuppurative cervical adenitis and changes in the skin and mucous membranes such as edema; congested conjunctivae; erythema of the oral cavity, lips, and palms; and desquamation of the skin of the fingertips. Although the disease is generally benign and self-limited, it is associated with coronary artery aneurysms in ~25% of cases, with an overall case-fatality rate of 0.5–2.8%. These complications usually occur between the third and fourth weeks of illness during the convalescent stage. Vasculitis of the coronary arteries is seen in almost all the fatal cases that have been autopsied. There is typical intimal proliferation and infiltration of the vessel wall with mononuclear cells. Beadlike aneurysms and thromboses may be seen along the artery. Other manifestations include pericarditis, myocarditis, myocardial ischemia and infarction, and cardiomegaly.

Apart from the up to 2.8% of patients who develop fatal complications, the prognosis of this disease for uneventful recovery is excellent. High-dose IV γ globulin (2 g/kg as a single infusion over 10 h) together with aspirin (100 mg/kg per day for 14 days followed by 3–5 mg/kg per day for several weeks) have been shown to be effective in reducing the prevalence of coronary artery abnormalities when administered early in the course of the disease. Surgery may be necessary for Kawasaki disease patients that have giant coronary artery aneurysms or other coronary complications. Surgical treatment most commonly includes thromboendarterectomy, thrombus clearing, aneurysmal reconstruction, and coronary artery bypass grafting.

POLYANGIITIS OVERLAP SYNDROMES

Some patients with systemic vasculitis manifest clinicopathologic characteristics that do not fit precisely into any specific disease but have overlapping features of different vasculitides. Active systemic vasculitis in such settings has the same potential for causing irreversible organ system damage as when it occurs in one of the defined syndromes listed in Table 11-1. The diagnostic and therapeutic considerations as well as the prognosis for these patients depend on the sites and severity of active vasculitis. Patients with vasculitis that could potentially cause irreversible damage to a major organ system should be treated as described under "Granulomatosis With Polyangiitis (Wegener's)."

SECONDARY VASCULITIS

DRUG-INDUCED VASCULITIS

Vasculitis associated with drug reactions usually presents as palpable purpura that may be generalized or limited to the lower extremities or other dependent areas; however, urticarial lesions, ulcers, and hemorrhagic blisters may also occur. Signs and symptoms may be limited to the skin, although systemic manifestations such as fever, malaise, and polyarthralgias may occur. Although the skin is the predominant organ involved, systemic vasculitis may result from drug reactions. Drugs that have been implicated in vasculitis include allopurinol, thiazides, gold, sulfonamides, phenytoin, and penicillin.

An increasing number of drugs have been reported to cause vasculitis associated with antimyeloperoxidase ANCA. Of these, the best evidence of causality exists for hydralazine and propylthiouracil. The clinical manifestations in ANCA-positive drug-induced vasculitis can range from cutaneous lesions to glomerulonephritis and pulmonary hemorrhage. Outside of drug discontinuation, treatment should be based on the severity of the vasculitis. Patients with immediately life-threatening small-vessel vasculitis should initially be treated with glucocorticoids and cyclophosphamide as described for granulomatosis with polyangiitis (Wegener's). Following clinical improvement, consideration may be given for tapering such agents along a more rapid schedule.

SERUM SICKNESS AND SERUM SICKNESS–LIKE REACTIONS

These reactions are characterized by the occurrence of fever, urticaria, polyarthralgias, and lymphadenopathy 7–10 days after primary exposure and 2–4 days after secondary exposure to a heterologous protein (classic serum sickness) or a nonprotein drug such as penicillin or sulfa (serum sickness–like reaction). Most of the manifestations are not due to a vasculitis; however, occasional patients will have typical cutaneous venulitis that may progress rarely to a systemic vasculitis.

VASCULITIS ASSOCIATED WITH OTHER UNDERLYING DISEASES

Certain *infections* may directly trigger an inflammatory vasculitic process. For example, rickettsias can invade and proliferate in the endothelial cells of small blood vessels causing a vasculitis. In addition, the inflammatory

response around blood vessels associated with certain systemic fungal diseases such as histoplasmosis may mimic a primary vasculitic process. A leukocytoclastic vasculitis predominantly involving the skin with occasional involvement of other organ systems may be a minor component of many other infections. These include *subacute bacterial endocarditis*, *Epstein-Barr virus infection*, *HIV infection*, as well as a number of other infections.

Vasculitis can be associated with certain *malignancies*, particularly lymphoid or reticuloendothelial neoplasms. Leukocytoclastic venulitis confined to the skin is the most common finding; however, widespread systemic vasculitis may occur. Of particular note is the association of *hairy cell leukemia* with PAN.

A number of *connective tissue diseases* have vasculitis as a secondary manifestation of the underlying primary process. Foremost among these are *systemic lupus erythematosus* (Chap. 4), *rheumatoid arthritis* (Chap. 6), *inflammatory myositis* (Chap. 17), *relapsing polychondritis* (Chap. 13), and *Sjögren's syndrome* (Chap. 9). The most common form of vasculitis in these conditions is the small-vessel venulitis isolated to the skin. However, certain patients may develop a fulminant systemic necrotizing vasculitis.

Secondary vasculitis has also been observed in association with *ulcerative colitis*, *congenital deficiencies of various complement components*, *retroperitoneal fibrosis*, *primary biliary cirrhosis*, α_1*-antitrypsin deficiency*, and *intestinal bypass surgery*.

CHAPTER 12

BEHÇET'S DISEASE

Haralampos M. Moutsopoulos

DEFINITION, INCIDENCE, AND PREVALENCE

Behçet's disease is a multisystem disorder presenting with recurrent oral and genital ulcerations as well as ocular involvement. The diagnosis is clinical and based on internationally agreed diagnostic criteria (Table 12-1).

The disease affects young males and females from the Mediterranean region, the Middle East, and the Far East, suggesting a link with the ancient Silk Route. Males and females are affected equally, but males often have more severe disease. Blacks are very infrequently affected.

PATHOGENESIS

The etiology and pathogenesis of this syndrome remain obscure. The main pathologic lesion is systemic perivasculitis with early neutrophil infiltration and endothelial swelling. In some patients, diffuse inflammatory disease, involving all layers of large vessels and resulting to formation of pseudoaneurysms, suggests vasculitis of vasa vasorum. Apart from neutrophils, increased numbers of infiltrating CD4+ T cells are observed. Circulating autoantibodies against α-enolase of endothelial cells, selenium binding protein and anti-*Saccharomyces cerevisiae antibodies* (ASCA—characteristic of Crohn's A recent genome-wide association study, confirmed the known association of Behçet's disease with HLA-B*51 and identified a second, independent association within the MHC Class I region. In addition, an association with IL10 and the IL23R-IL12RB2 locus were also observed. Interestingly, the disease-associated IL10 variant was correlated with diminished mRNA expression and low protein production.

TABLE 12-1

DIAGNOSTIC CRITERIA OF BEHÇET'S DISEASE
Recurrent oral ulceration plus two of the following:
Recurrent genital ulceration
Eye lesions
Skin lesions
Pathergy test

CLINICAL FEATURES

The recurrent aphthous ulcerations are a sine qua non for the diagnosis. The ulcers are usually painful, are shallow or deep with a central yellowish necrotic base, appear singly or in crops, and are located anywhere in the oral cavity. Small ulcers, less than 10 mm in diameter are seen in 85% of patients, while large or herpetiform lesions are less frequent. The ulcers persist for 1–2 weeks and subside without leaving scars. The genital ulcers are less common but more specific, are painful, do not affect the glans penis or urethra, and produce scrotal scars.

Skin involvement is observed in 80% of patients and includes folliculitis, erythema nodosum, an acne-like exanthem, and, infrequently, vasculitis, Sweet's syndrome, and pyoderma gangrenosum. Nonspecific skin inflammatory reactivity to any scratches or intradermal saline injection (pathergy test) is a common and specific manifestation.

Eye involvement with scarring and bilateral panuveitis is the most dreaded complication, since it occasionally progresses rapidly to blindness. The eye disease, occurring in 50% of patients, is usually present at the onset but may also develop within the first few years. In addition to iritis, posterior uveitis, retinal vessel occlusions, and optic neuritis can be seen in some patients with the syndrome.

Non-deforming arthritis or arthralgias are seen in a 50% of patients and affects the knees and ankles.

Superficial or deep peripheral vein thrombosis is seen in 30% of patients. Pulmonary emboli are a rare

complication. The superior vena cava is obstructed occasionally, producing a dramatic clinical picture. Arterial involvement occurs in less than 5% of patients and presents with aortitis or peripheral arterial aneurysm and arterial thrombosis. Pulmonary artery vasculitis presenting with dyspnea, cough, chest pain, hemoptysis, and infiltrates on chest roentgenograms has been reported in 5% of patients and should be differentiated from thromboembolic disease since it warrants anti-inflammatory and not thrombolytic therapy.

Neurologic involvement (5–10%) appears mainly in the parenchymal form (80%); it is associated with brainstem involvement and has a serious prognosis (*CNS-Behçet's disease*). IL-6 is persistently raised in cerebrospinal fluid of these patients. Dural sinus thrombi (20%) are associated with headache and increased intracranial pressure. MRI and/or proton magnetic resonance spectroscopy (MRS) are very sensitive and should be employed if CNS-Behçet's disease is suspected.

Gastrointestinal involvement is seen more frequently in patients from Japan and consists of mucosal ulcerations of the gut, resembling Crohn's disease.

Epididymitis is seen in 5% of patients, while amyloidosis of AA type and glomerulonephritis are uncommon.

Laboratory findings are mainly nonspecific indices of inflammation, such as leukocytosis and elevated erythrocyte sedimentation rate, as well as C-reactive protein levels.

TREATMENT **Behçet's Disease**

The severity of the syndrome usually abates with time. Apart from the patients with CNS-Behçet's disease and major vessel disease, the life expectancy seems to be normal and the only serious complication is blindness.

Mucous membrane involvement may respond to topical glucocorticoids in the form of mouthwash or paste. In more serious cases, thalidomide (100 mg/d) is effective. Thrombophlebitis is treated with aspirin, 325 mg/d. Colchicine can be beneficial for the mucocutaneous manifestations and arthritis. Uveitis and CNS-Behçet's disease require systemic glucocorticoid therapy (prednisone, 1 mg/kg per day) and azathioprine (2–3 mg/kg per day). Cyclosporin (5mg/kg) has been used for sight-threatening uveitis, alone or in combination with azathioprine. Pulse doses of cyclophosphamide are useful early in the course of the disease, for pulmonary or peripheral arterial aneurysms. Recent recommendations for anti–tumor necrosis factor therapy suggest that they may serve as an add-on immunosuppressive therapy in patients with panuveitis refractory or intolerant to other immunosuppressives.

CHAPTER 13

RELAPSING POLYCHONDRITIS

Carol A. Langford

Relapsing polychondritis is an uncommon disorder of unknown cause characterized by inflammation of cartilage predominantly affecting the ears, nose, and laryngotracheobronchial tree. Other manifestations include scleritis, neurosensory hearing loss, polyarthritis, cardiac abnormalities, skin lesions, and glomerulonephritis. Relapsing polychondritis has been estimated to have an incidence of 3.5 per million population per year. The peak age of onset is between the ages of 40–50 years, but relapsing polychondritis may affect children and the elderly. It is found in all races, and both sexes are equally affected. No familial tendency is apparent. A significantly higher frequency of HLA-DR4 has been found in patients with relapsing polychondritis than in healthy individuals. A predominant subtype allele(s) of HLA-DR4 was not found. Approximately 30% of patients with relapsing polychondritis will have another rheumatologic disorder, the most frequent being systemic vasculitis, followed by rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, or the spondyloarthritides. Nonrheumatic disorders associated with relapsing polychondritis include inflammatory bowel disease, primary biliary cirrhosis, and myelodysplastic syndrome (Table 13-1). In most cases, these disorders antedate the appearance of relapsing polychondritis, usually by months or years.

TABLE 13-1

DISORDERS ASSOCIATED WITH RELAPSING POLYCHONDRITIS[a]
Systemic vasculitis
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren's syndrome
Spondyloarthritides
Behçet's disease
Inflammatory bowel disease
Primary biliary cirrhosis
Myelodysplastic syndrome

[a]Systemic vasculitis is the most common association followed by rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome.
Source: Modified from CJ Michet et al: Ann Intern Med 104:74, 1986.

PATHOLOGY AND PATHOPHYSIOLOGY

The earliest abnormality of hyaline and elastic cartilage noted histologically is a focal or diffuse loss of basophilic staining indicating depletion of proteoglycan from the cartilage matrix. Inflammatory infiltrates are found adjacent to involved cartilage and consist predominantly of mononuclear cells and occasional plasma cells. In acute disease, polymorphonuclear white cells may also be present. Destruction of cartilage begins at the outer edges and advances centrally. There is lacunar breakdown and loss of chondrocytes. Degenerating cartilage is replaced by granulation tissue and later by fibrosis and focal areas of calcification. Small loci of cartilage regeneration may be present. Immunofluorescence studies have shown immunoglobulins and complement at sites of involvement. Extracellular granular material observed in the degenerating cartilage matrix by electron microscopy has been interpreted to be enzymes, immunoglobulins, or proteoglycans.

Immunologic mechanisms play a role in the pathogenesis of relapsing polychondritis. The accumulating data strongly suggest that both humoral and cell-mediated immunity play an important role in the pathogenesis of relapsing polychondritis. Immunoglobulin and complement deposits are found at sites of inflammation. In addition, antibodies to type II collagen and to matrilin-1 and immune complexes are detected in the sera of some patients. The possibility that an immune response to type II collagen may be important in the pathogenesis is supported experimentally by the occurrence of

auricular chondritis in rats immunized with type II collagen. Antibodies to type II collagen are found in the sera of these animals, and immune deposits are detected at sites of ear inflammation. Humoral immune responses to type IX and type XI collagen, matrilin-1, and cartilage oligomeric matrix protein have been demonstrated in some patients. In a study, rats immunized with matrilin-1 were found to develop severe inspiratory stridor and swelling of the nasal septum. The rats had severe inflammation with erosions of the involved cartilage, which was characterized by increased numbers of CD4+ and CD8+ T cells in the lesions. The cartilage of the joints and ear pinna was not involved. All had IgG antibodies to matrilin-1. Matrilin-1 is a noncollagenous protein present in the extracellular matrix in cartilage. It is present in high concentrations in the trachea and is also present in the nasal septum but not in articular cartilage. A subsequent study demonstrated serum anti-matrilin-1 antibodies in approximately 13% of patients with relapsing polychondritis; approximately 70% of these patients had respiratory symptoms. Cell-mediated immunity may also be operative in causing tissue injury, since lymphocyte transformation can be demonstrated when lymphocytes of patients are exposed to cartilage extracts. T cells specific for type II collagen have been found in some patients, and CD4+ T cells have been observed at sites of cartilage inflammation.

CLINICAL MANIFESTATIONS

The onset of relapsing polychondritis is frequently abrupt with the appearance of one or two sites of cartilaginous inflammation. The pattern of cartilaginous involvement and the frequency of episodes vary widely among patients. Non-cartilaginous presentations may also occur. Systemic inflammatory features such as fever, fatigue, and weight loss occur and may precede the clinical signs of relapsing polychondritis by several weeks. Relapsing polychondritis may go unrecognized for several months or even years in patients who only initially manifest intermittent joint pain and/or swelling, or who have unexplained eye inflammation, hearing loss, valvular heart disease, or pulmonary symptoms.

Auricular chondritis is the most frequent presenting manifestation of relapsing polychondritis occurring in 40% of patients and eventually affecting about 85% of patients (Table 13-2). One or both ears are involved, either sequentially or simultaneously. Patients experience the sudden onset of pain, tenderness, and swelling of the cartilaginous portion of the ear (Fig. 13-1). This typically involves the pinna of the ears, sparing the earlobes because they do not contain cartilage. The overlying skin has a beefy red or violaceous color. Prolonged or recurrent episodes lead to cartilage destruction and result in a flabby or droopy ear. Swelling may close off the eustachian tube or the external auditory meatus, either of which can impair hearing. Inflammation of the internal auditory artery or its cochlear branch produces hearing loss, vertigo, ataxia, nausea, and vomiting. Vertigo is almost always accompanied by hearing loss.

Approximately 61% of patients will develop nasal involvement, with 21% having this at the time of

TABLE 13-2

CLINICAL MANIFESTATIONS OF RELAPSING POLYCHONDRITIS

CLINICAL FEATURE	PRESENTING	CUMULATIVE
	Frequency, %	
Auricular chondritis	43	89
Arthritis	32	72
Nasal chondritis	21	61
Ocular inflammation	18	59
Laryngotracheal symptoms	23	55
Reduced hearing	7	40
Saddle nose deformity	11	25
Cutaneous	4	25
Laryngotracheal stricture	15	23
Vasculitis	2	14
Elevated creatinine	7	13
Aortic or mitral regurgitation	0	12

Source: Modified from PD Kent et al: Curr Opin Rheumatol 16:56, 2004.

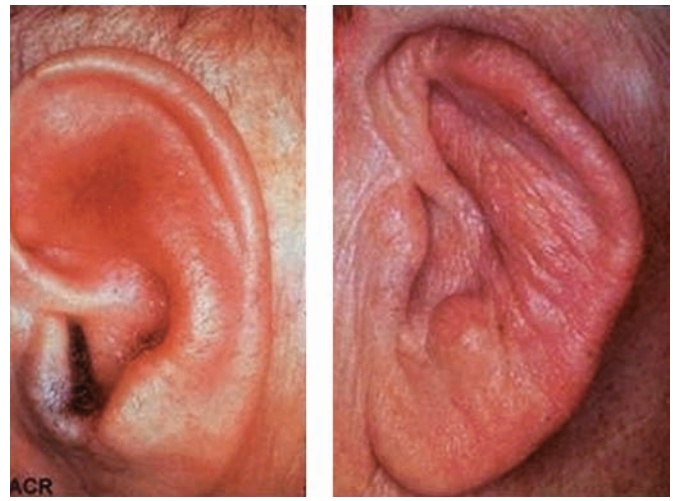


FIGURE 13-1

Left. The pinna is erythematous, swollen, and tender. Not shown is the ear lobule that is spared as there is no underlying cartilage. ***Right***. The pinna is thickened and deformed. The destruction of the underlying cartilage results in a floppy ear. (*Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, ©1991, 1995, 1997, 1998, 1999. Used by permission of the American College of Rheumatology.*)

presentation. Patients may experience nasal stuffiness, rhinorrhea, and epistaxis. The bridge of the nose and surrounding tissue becomes red, swollen, and tender and may collapse, producing a saddlenose deformity **(Fig. 13-2)**. In some patients, nasal deformity develops insidiously without overt inflammation. Saddlenose is observed more frequently in younger patients, especially in women.

Joint involvement is the presenting manifestation in relapsing polychondritis in approximately one-third of patients and may be present for several months before other features appear. Eventually, more than one-half of the patients will have arthralgias or arthritis. The arthritis is usually asymmetric and oligo- or polyarticular, and it involves both large and small peripheral joints. An episode of arthritis lasts from a few days to several weeks and resolves spontaneously without joint erosion or deformity. Attacks of arthritis may not be temporally related to other manifestations of relapsing polychondritis. Joint fluid has been reported to be noninflammatory. In addition to peripheral joints, inflammation may involve the costochondral, sternomanubrial, and sternoclavicular cartilages. Destruction of these cartilages may result in a pectus excavatum deformity or even a flail anterior chest wall.

Eye manifestations occur in more than one-half of patients and include conjunctivitis, episcleritis, scleritis, iritis, uveitis, and keratitis. Ocular inflammation can be severe and visually threatening. Other manifestations include eyelid and periorbital edema, proptosis, optic neuritis, extraocular muscle palsies, retinal vasculitis, and renal vein occlusion.



FIGURE 13-2
Saddlenose results from destruction and collapse of the nasal cartilage. (*Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, ©1991, 1995, 1997, 1998, 1999. Used by permission of the American College of Rheumatology.*)

Laryngotracheobronchial involvement occurs in ~50% of patients and is among the most serious manifestations of relapsing polychondritis. Symptoms include hoarseness, a nonproductive cough, and tenderness over the larynx and proximal trachea. Mucosal edema, strictures, and/or collapse of laryngeal or tracheal cartilage may cause stridor and life-threatening airway obstruction necessitating tracheostomy. Involvement can extend into the lower airways resulting in tracheobronchomalacia. Collapse of cartilage in bronchi leads to pneumonia and, when extensive, to respiratory insufficiency.

Cardiac valvular regurgitation occurs in about 5–10% of patients and is due to progressive dilation of the valvular ring or to destruction of the valve cusps. Aortic regurgitation occurs in about 7% of patients with the mitral and other heart valves being affected less often. Other cardiac manifestations include pericarditis, myocarditis, coronary vasculitis, and conduction abnormalities. Aneurysms of the proximal, thoracic, or abdominal aorta may occur even in the absence of active chondritis and occasionally rupture.

Renal disease occurs in about 10% of patients. The most common renal lesions include mesangial expansion or segmental necrotizing glomerulonephritis, which have been reported to have small amounts of electron-dense deposits in the mesangium where there is also faint deposition of C3 and/or IgG or IgM. Tubulointerstitial disease and IgA nephropathy have also been reported.

Approximately 25% of patients have skin lesions, which can include purpura, erythema nodosum, erythema multiforme, angioedema/urticaria, livedo reticularis, and panniculitis.

Features of vasculitis are seen in up to 25% of patients and can affect any size vessel. Large vessel vasculitis may present with aortic aneurysms and medium vessel disease may affect the coronary, hepatic, mesenteric, or renal arteries or vessel supplying nerves. Skin vessel disease and involvement of the postcapillary venules can also occur. A variety of primary vasculitides have also been reported to occur in association with relapsing polychondritis (Chap. 11). One specific overlap is the "MAGIC" syndrome (*m*outh *a*nd *g*enital ulcers with *i*nflamed *c*artilage) in which patients present with features of both relapsing polychondritis and Behçet's disease (Chap. 12).

LABORATORY FINDINGS AND DIAGNOSTIC IMAGING

There are no laboratory features that are diagnostic for relapsing polychondritis. Mild leukocytosis and normocytic, normochromic anemia are often present. Eosinophilia is observed in 10% of patients. The erythrocyte

sedimentation rate and C-reactive protein are usually elevated. Rheumatoid factor and antinuclear antibody tests are occasionally positive in low titers and complement levels are normal. Antibodies to type II collagen are present in fewer than one-half of the patients and are not specific. Circulating immune complexes may be detected, especially in patients with early active disease. Elevated levels of γ globulin may be present. Antineutrophil cytoplasmic antibodies (ANCA), either cytoplasmic (cANCA) or perinuclear (pANCA), are found in some patients with active disease. However, on target antigen specific testing, there are only occasional reports of positive myeloperoxidase-ANCA and proteinase 3-ANCA are very rarely found in relapsing polychondritis.

The upper and lower airways can be evaluated by imaging techniques such as computed tomography and magnetic resonance imaging. Bronchoscopy provides direct visualization of the airways but can be a high-risk procedure in patients with airway compromise. Pulmonary function testing with flow-volume loops can show inspiratory and/or expiratory obstruction. Imaging can also be useful to detect extracartilaginous disease. The chest film may show widening of the ascending or descending aorta due to an aneurysm, and cardiomegaly when aortic insufficiency is present. MRI can assess aortic aneurysmal dilatation. Electrocardiography and echocardiography can be useful in further evaluating for cardiac features of disease.

DIAGNOSIS

Diagnosis is based on recognition of the typical clinical features. Biopsies of the involved cartilage from the ear, nose, or respiratory tract will confirm the diagnosis but are only necessary when clinical features are not typical. Diagnostic criteria were suggested in 1976 by McAdam et al and modified by Damiani and Levine in 1979. These criteria continue to be generally used in clinical practice. McAdam et al proposed the following: (1) recurrent chondritis of both auricles; (2) nonerosive inflammatory arthritis; (3) chondritis of nasal cartilage; (4) inflammation of ocular structures, including conjunctivitis, keratitis, scleritis/episcleritis, and/or uveitis; (5) chondritis of the laryngeal and/or tracheal cartilages; and (6) cochlear and/or vestibular damage manifested by neurosensory hearing loss, tinnitus, and/or vertigo. The diagnosis is certain when three or more of these features are present along with a positive biopsy from the ear, nasal, or respiratory cartilage. Damiani and Levine later suggested that the diagnosis could be made when one or more of the above features and a positive biopsy were present, when two or more separate sites of cartilage inflammation were present that responded to glucocorticoids or dapsone, or when three or more of the above features were present.

The differential diagnosis of relapsing polychondritis is centered around its sites of clinical involvement. Patients with granulomatosis with polyangiitis (Wegener's) may have a saddlenose and tracheal involvement but can be distinguished by the primary inflammation occurring in the mucosa at these sites, the absence of auricular involvement, and the presence of pulmonary parenchymal disease. Patients with Cogan's syndrome have interstitial keratitis and vestibular and auditory abnormalities, but this syndrome does not involve the respiratory tract or ears. Reactive arthritis may initially resemble relapsing polychondritis because of oligoarticular arthritis and eye involvement, but it is distinguished in time by the appearance of urethritis and typical mucocutaneous lesions and the absence of nose or ear cartilage involvement. Rheumatoid arthritis may initially suggest relapsing polychondritis because of arthritis and eye inflammation. The arthritis in rheumatoid arthritis, however, is erosive and symmetric. In addition, rheumatoid factor titers are usually high compared with those in relapsing polychondritis and anti-cyclic citrullinated peptide is usually not seen. Bacterial infection of the pinna may be mistaken for relapsing polychondritis but differs by usually involving only one ear, including the earlobe. Auricular cartilage may also be damaged by trauma or frostbite.

TREATMENT Relapsing Polychondritis

In patients with active chondritis, prednisone, 40–60 mg/d, is often effective in suppressing disease activity; it is tapered gradually once disease is controlled. In some patients, prednisone can be stopped, while in others low doses in the range of 5–10 mg/d are required for continued suppression of disease. Dapsone 50–100 mg/d has been effective for cartilage inflammation and joint features in some patients. Other immunosuppressive drugs such as cyclophosphamide, methotrexate, azathioprine, or cyclosporine should be reserved for patients who have severe organ-threatening disease, fail to respond to prednisone, or who require high doses for control of disease activity. Patients with significant ocular inflammation often require intraocular glucocorticoids as well as high doses of prednisone. There are a small number of reports on the use of tumor necrosis factor antagonists, which are too few in number to assess efficacy. A small retrospective series of nine patients did not find anti-CD20 (rituximab) to provide benefit although this experience remains too small to draw firm conclusions. Heart valve replacement or repair of an aortic aneurysm may be necessary. When obstruction is severe, tracheostomy is required.

Stents may be necessary in patients with tracheobronchial collapse.

PATIENT OUTCOME, PROGNOSIS, AND SURVIVAL

The course of relapsing polychondritis is highly variable, with inflammatory episodes lasting from a few days to several weeks and then subsiding spontaneously. Attacks may recur at intervals varying from weeks to months. In other patients, the disease has a chronic, smoldering course. In a few patients, the disease may be limited to one or two episodes of cartilage inflammation. In one study, the 5-year estimated survival rate was 74% and the 10-year survival rate 55%. In contrast to earlier series, only about one-half of the deaths could be attributed to relapsing polychondritis or complications of treatment. Pulmonary complications accounted for only 10% of all fatalities. In general, patients with more widespread disease have a worse prognosis.

ACKNOWLEDGMENT

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CHAPTER 14

SARCOIDOSIS

Robert P. Baughman ■ Elyse E. Lower

DEFINITION

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas. The disease is often multisystem and requires the presence of involvement in two or more organs for a specific diagnosis. The finding of granulomas is not specific for sarcoidosis, and other conditions known to cause granulomas must be ruled out. These conditions include mycobacterial and fungal infections, malignancy, and environmental agents such as beryllium. While sarcoidosis can affect virtually every organ of the body, the lung is most commonly affected. Other organs commonly affected are the liver, skin, and eye. The clinical outcome of sarcoidosis varies, with remission occurring in over one-half of the patients within a few years of diagnosis; however, the remaining patients may develop a chronic disease that lasts for decades.

ETIOLOGY

Despite multiple investigations, the cause of sarcoidosis remains unknown. Currently, the most likely etiology is an infectious or noninfectious environmental agent that triggers an inflammatory response in a genetically susceptible host. Among the possible infectious agents, careful studies have shown a much higher incidence of *Propionibacter acnes* in the lymph nodes of sarcoidosis patients compared to controls. An animal model has shown that *P. acnes* can induce a granulomatous response in mice similar to sarcoidosis. Others have demonstrated the presence of a mycobacterial protein (*Mycobacterium tuberculosis* catalase-peroxidase [mKatG]) in the granulomas of some sarcoidosis patients. This protein is very resistant to degradation and may represent the persistent antigen in sarcoidosis. Immune response to this and other mycobacterial proteins has been documented by another laboratory. These studies suggest that a mycobacterium similar to *M. tuberculosis* could be responsible for sarcoidosis. The mechanism exposure/infection with such agents has been the focus of other studies. Environmental exposures to insecticides and mold have been associated with an increased risk for disease. In addition, health care workers appear to have an increased risk. Also, sarcoidosis in a donor organ has occurred after transplantation into a sarcoidosis patient. Some authors have suggested that sarcoidosis is not due to a single agent but represents a particular host response to multiple agents. Some studies have been able to correlate the environmental exposures to genetic markers. These studies have supported the hypothesis that a genetically susceptible host is a key factor in the disease.

INCIDENCE AND PREVALENCE



Sarcoidosis is seen worldwide, with the highest prevalence reported in the Nordic population. In the United States, the disease has been reported more commonly in African Americans than whites, with the ratio of African Americans to whites ranging from 3:1 to 17:0. Women appear to be slightly more susceptible than men. The lower estimate is from a large health maintenance organization in Detroit. The earlier American studies finding the higher incidence in African Americans may have been influenced by the fact that African Americans seem to develop more extensive and chronic pulmonary disease. Since most sarcoidosis clinics are run by pulmonologists, a selection bias may have occurred. Worldwide, the prevalence of the disease varies from 20–60 per 100,000 for many groups such as Japanese, Italians, and American whites. Higher rate occurs in Ireland and Nordic countries. In one closely observed community in Sweden, the lifetime risk for developing sarcoidosis was 3%.

Sarcoidosis often occurs in young, otherwise healthy adults. It is uncommon to diagnose the disease in someone under age 18. However, it has become clear that a second peak in incidence develops around age 60. In a study of >700 newly diagnosed sarcoidosis patients in the United States, one-half of the patients were ≥40 years at the time of diagnosis.

Although most cases of sarcoidosis are sporadic, a familial form of the disease exists. At least 5% of patients with sarcoidosis will have a family member with sarcoidosis. Sarcoidosis patients who are Irish or African American seem to have a two to three times higher rate of familial disease.

PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS

The granuloma is the pathologic hallmark of sarcoidosis. A distinct feature of sarcoidosis is the local accumulation of inflammatory cells. Extensive studies in the lung using bronchoalveolar lavage (BAL) have demonstrated that the initial inflammatory response is an influx of T helper cells. In addition, there is an accumulation of activated monocytes. **Figure 14-1** is a proposed model for sarcoidosis. Using the HLA-CD4 complex, antigen-presenting cells present an unknown antigen to the helper T cell. Studies have clarified that specific HLA haplotypes such as HLA-DRB1*1101 are associated with an increased risk for developing sarcoidosis. In addition, different HLA haplotypes are associated with different clinical outcomes.

The macrophage/helper T cell cluster leads to activation with the increased release of several cytokines. These include interleukin (IL)-2 released from the T cell and interferon γ and tumor necrosis factor (TNF) released by the macrophage. The T cell is a necessary part of the initial inflammatory response. In advanced, untreated HIV infection, patients who lack helper T cells rarely develop sarcoidosis. In contrast, several reports confirm that sarcoidosis becomes unmasked as HIV-infected individuals receive antiretroviral therapy, with subsequent restoration of their immune system. In contrast, treatment of established pulmonary sarcoidosis with cyclosporine, a drug that downregulates helper T cell responses, seems to have little impact on sarcoidosis.

The granulomatous response of sarcoidosis can resolve with or without therapy. However, in at least 20% of patients with sarcoidosis, a chronic form of the disease develops. This persistent form of the disease is associated with the secretion of high levels of IL-8. Also, studies have reported that in patients with this chronic form of disease excessive amounts of TNF are released in the areas of inflammation.

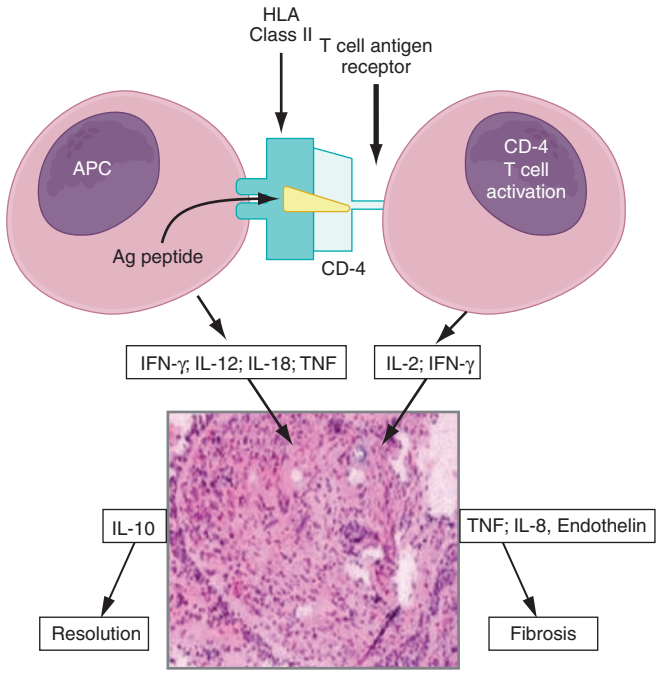


FIGURE 14-1

Schematic representation of initial events of sarcoidosis. The antigen-presenting cell and helper T cell complex leads to the release of multiple cytokines. This forms a granuloma. Over time, the granuloma may resolve or lead to chronic disease, including fibrosis. APC, antigen-presenting cell; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

It is sometimes difficult to determine early on the ultimate clinical outcome of sarcoidosis. One form of the disease, *Löfgren's syndrome*, consists of erythema nodosum, hilar adenopathy on chest roentgenogram, and uveitis. Löfgren's syndrome is associated with a good prognosis, with >90% of patients experiencing disease resolution within 2 years. A recently proposed expansion of the term Lofgren's syndrome includes periarticular arthritis without erythema nodosum. Recent studies have demonstrated that the HLA-DRB1*03 was found in two-thirds of Scandinavian patients with Löfgren's syndrome. More than 95% of those patients who were HLA-DRB1*03 positive had resolution of their disease within 2 years, while nearly one-half of the remaining patients had disease for more than 2 years. It remains to be determined whether these observations can be applied to a non-Scandinavian population.

CLINICAL MANIFESTATIONS

The presentation of sarcoidosis ranges from patients who are asymptomatic to those with organ failure. It is unclear how often sarcoidosis is asymptomatic.

In countries where routine chest roentgenogram screening is performed, 20–30% of pulmonary cases are detected in asymptomatic individuals. The inability to screen for other asymptomatic forms of the disease would suggest that as many as one-third of sarcoidosis patients are asymptomatic.

Respiratory complaints including cough and dyspnea are the most common presenting symptoms. In many cases, the patient presents with a 2–4 week history of these symptoms. Unfortunately, due to the nonspecific nature of pulmonary symptoms, the patient may see physicians for up to a year before a diagnosis is confirmed. For these patients, the diagnosis of sarcoidosis is usually only suggested when a chest roentgenogram is performed.

Symptoms related to cutaneous and ocular disease are the next two most common complaints. Skin lesions are often nonspecific. However, since these lesions are readily observed, the patient and treating physician are often led to a diagnosis. In contrast to patients with pulmonary disease, patients with cutaneous lesions are more likely to be diagnosed within 6 months of symptoms.

Nonspecific constitutional symptoms include fatigue, fever, night sweats, and weight loss. Fatigue is perhaps the most common constitutional symptom that affects these patients. Given its insidious nature, patients are usually not aware of the association with their sarcoidosis until their disease resolves.

The overall incidence of sarcoidosis at the time of diagnosis and eventual common organ involvement are summarized in **Table 14-1**. Over time, skin, eye, and neurologic involvement seem more apparent. In the United States, the frequency of specific organ involvement appears to be affected by age, race, and gender. For example, eye disease is more common among African Americans. Under the age of 40, it occurs more frequently in women. However, in those diagnosed over the age of 40, eye disease is more common in men.

TABLE 14-1

FREQUENCY OF COMMON ORGAN INVOLVEMENT AND LIFETIME RISK[a]

	PRESENTATION, %[b]	FOLLOW-UP, %[c]
Lung	95	94
Skin	24	43
Eye	12	29
Extrathoracic lymph node	15	16
Liver	12	14
Spleen	7	8
Neurologic	5	16
Cardiac	2	3

[a]Patients could have more than one organ involved.
[b]From ACCESS study of 736 patients evaluated. within 6 months of diagnosis.
[c]From follow-up of 1024 sarcoidosis patients seen at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis Clinic from 2002–2006.

LUNG

Lung involvement occurs in >90% of sarcoidosis patients. The most commonly used method for detecting lung disease is still the chest roentgenogram. **Figure 14-2** illustrates the chest roentgenogram from a sarcoidosis patient with bilateral hilar adenopathy. Although the CT scan has changed the diagnostic approach to interstitial lung disease, the CT scan is not usually considered a monitoring tool for patients with sarcoidosis. **Figure 14-3** demonstrates some of the characteristic CT features, including peribronchial thickening and reticular nodular changes, which are predominantly subpleural. The peribronchial thickening seen on CT scan seems to explain the high yield of granulomas from bronchial biopsies performed for diagnosis.

While the CT scan is more sensitive, the standard scoring system described by Scadding in 1961 for chest roentgenograms remains the preferred method of characterizing the chest involvement. Stage 1 is hilar adenopathy alone (Fig. 14-2), often with right paratracheal involvement. Stage 2 is a combination of adenopathy plus infiltrates, whereas stage 3 reveals infiltrates alone. Stage 4 consists of fibrosis. Usually the infiltrates in sarcoidosis are predominantly an upper lobe process. Only in a few noninfectious diseases is an upper lobe predominance noted. In addition to sarcoidosis,



FIGURE 14-2
Posterior-anterior chest roentgenogram demonstrating bilateral hilar adenopathy, stage 1 disease.



FIGURE 14-3
High-resolution CT scan of chest demonstrating patchy reticular nodularity, including areas of confluence.

the differential diagnosis of upper lobe disease includes hypersensitivity pneumonitis, silicosis, and Langerhans cell histiocytosis. For infectious diseases, tuberculosis and *Pneumocystis* pneumonia can often present as upper lobe diseases.

Lung volumes, mechanics, and diffusion all are useful in evaluating interstitial lung diseases such as sarcoidosis. The diffusion of carbon monoxide (DLCO) is the most sensitive test for an interstitial lung disease. Reduced lung volumes are a reflection of the restrictive lung disease seen in sarcoidosis. However, a third of the patients presenting with sarcoidosis still have lung volumes within the normal range, despite abnormal chest roentgenograms and dyspnea.

Approximately one-half of sarcoidosis patients present with obstructive disease, reflected by a reduced ratio of forced vital capacity expired in one second (FEV_1/FVC). Cough is a very common symptom. Airway involvement causing varying degrees of obstruction underlies the cough in most sarcoidosis patients. Airway hyperreactivity as determined by methacholine challenge will be positive in some of these patients. A few patients with cough will respond to traditional bronchodilators as the only form of treatment. In some cases, high-dose inhaled glucocorticoids alone are useful.

Pulmonary arterial hypertension is reported in at least 5% of sarcoidosis patients. Either direct vascular involvement or the consequence of fibrotic changes in the lung can lead to pulmonary arterial hypertension. In sarcoidosis patients with end-stage fibrosis awaiting lung transplant, 70% will have pulmonary arterial hypertension. This is a much higher incidence than that reported for other fibrotic lung diseases. In less advanced, but still symptomatic, patients pulmonary arterial hypertension has been noted in up to 50% of the cases. Because sarcoidosis-associated pulmonary arterial hypertension may respond to therapy, evaluation for this should be considered in persistently symptomatic patients.

SKIN

Skin involvement is eventually identified in over a third of patients with sarcoidosis. The classic cutaneous lesions include erythema nodosum, maculopapular lesions, hyper- and hypopigmentation, keloid formation, and subcutaneous nodules. A specific complex of involvement of the bridge of the nose, the area beneath the eyes, and the cheeks is referred to as *lupus pernio* **(Fig. 14-4)** and is diagnostic for a chronic form of sarcoidosis.

In contrast, erythema nodosum is a transient rash that can be seen in association with hilar adenopathy and uveitis (Löfgren's syndrome). Erythema nodosum is more common in women and in certain self-described demographic groups including whites and Puerto Ricans. In the United States, the other manifestations of skin sarcoidosis, especially lupus pernio, are more common in African Americans than whites.

The maculopapular lesions from sarcoidosis are the most common chronic form of the disease **(Fig. 14-5)**. These are often overlooked by the patient and physician, since they are chronic and not painful. Initially, these lesions are usually purplish papules and are often indurated. They can become confluent and infiltrate



FIGURE 14-4
Chronic inflammatory lesions around nose, eyes, and cheeks, referred to as lupus pernio.



FIGURE 14-5
Maculopapular lesions on the trunk of a sarcoidosis patient.

large areas of the skin. With treatment, the color and induration may fade. Because these lesions are caused by noncaseating granulomas, the diagnosis of sarcoidosis can be readily made by a skin biopsy.

EYE

The frequency of ocular manifestations for sarcoidosis varies depending on race. In Japan, >70% of sarcoidosis patients develop ocular disease, while in the United States only 30% have eye disease, with problems more common in African Americans than whites. Although the most common manifestation is an anterior uveitis, over a quarter of patients will have inflammation at the posterior of the eye, including retinitis and pars planitis. While symptoms such as photophobia, blurred vision, and increased tearing can occur, some asymptomatic patients still have active inflammation. Initially asymptomatic patients with ocular sarcoidosis can eventually develop blindness. Therefore, it is recommended that all patients with sarcoidosis receive a dedicated ophthalmologic examination. Sicca is seen in over one-half of the chronic sarcoidosis patients. Dry eyes appear to be a reflection of prior lacrimal gland disease. Although the patient may no longer have active inflammation, the dry eyes may require natural tears or other lubricants.

LIVER

Using biopsies to detect granulomatous disease, liver involvement can be identified in over one-half of sarcoidosis patients. However, using liver function studies, only 20–30% of patients will have evidence of liver involvement. The most common abnormality of liver function is an elevation of the alkaline phosphatase level, consistent with an obstructive pattern. In addition, elevated transaminase levels can occur. An elevated bilirubin level is a marker for more advanced liver disease. Overall, only 5% of sarcoidosis patients have sufficient symptoms from their liver disease to require specific therapy. Although symptoms can be due to hepatomegaly, more frequently symptoms result from extensive intrahepatic cholestasis leading to portal hypertension. In this case, ascites and esophageal varices can occur. It is rare that a sarcoidosis patient will require a liver transplant, because even the patient with cirrhosis due to sarcoidosis can respond to systemic therapy. On a cautionary note, patients with both sarcoidosis and hepatitis C should avoid therapy with interferon α because of its association with the development or worsening of granulomatous disease.

BONE MARROW AND SPLEEN

One or more bone marrow manifestations can be identified in many sarcoidosis patients. The most common hematologic problem is lymphopenia, which is a reflection of sequestration of the lymphocytes into the areas of inflammation. Anemia occurs in 20% of patients and leukopenia is less common. Bone marrow examination will reveal granulomas in about a third of patients. Splenomegaly can be detected in 5–10% of patients, but splenic biopsy reveals granulomas in 60% of patients. The CT scan can be relatively specific for sarcoidosis involvement of the spleen **(Fig. 14-6)**. Both bone marrow and spleen involvement are more common in

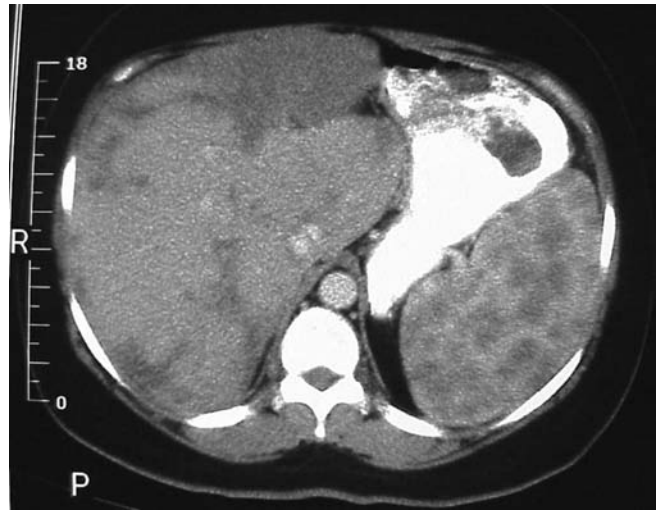


FIGURE 14-6
CT scan of the abdomen after oral and intravenous contrast. The stomach is compressed by the enlarged spleen. Within the spleen, areas of hypo- and hyperdensity are identified.

African Americans than whites. These manifestations alone are rarely an indication for therapy. On occasion, splenectomy may be indicated for massive symptomatic splenomegaly or profound pancytopenia.

CALCIUM METABOLISM

Hypercalcemia and/or hypercalciuria occurs in about 10% of sarcoidosis patients. It is more common in whites than African Americans and in men. The mechanism of abnormal calcium metabolism is increased production of 1,25-dihydroxyvitamin D by the granuloma itself. The 1,25-dihydroxyvitamin D causes increased intestinal absorption of calcium, leading to hypercalcemia with a suppressed parathyroid hormone (PTH) level. Increased exogenous vitamin D from diet or sunlight exposure may exacerbate this problem. Serum calcium should be determined as part of the initial evaluation of all sarcoidosis patients, and a repeat determination may be useful during the summer months with increased sun exposure. In patients with a history of renal calculi, a 24-h urine calcium measurement should be obtained. If a sarcoidosis patient with a history of renal calculi is to be placed on calcium supplements, a follow-up 24-h urine calcium level should be measured.

RENAL DISEASE

Direct kidney involvement occurs in <5% of sarcoidosis patients. It is associated with granulomas in the kidney itself and can lead to nephritis. However, hypercalcemia is the most likely cause of sarcoidosis-associated renal disease. In 1–2% of sarcoidosis patients, acute renal failure has been encountered as a result of hyper-calcemia. Treatment of the hypercalcemia with glucocorticoids and other therapies often improves, but does not totally resolve, the renal dysfunction.

NERVOUS SYSTEM

Neurologic disease is reported in 5–10% of sarcoidosis patients and appears to be of equal frequency across all ethnic groups. Any part of the central or peripheral nervous system can be affected. The presence of granulomatous inflammation is often visible on MRI studies. The MRI with gadolinium enhancement may demonstrate space-occupying lesions, but the MRI can be negative due to small lesions or the effect of systemic therapy in reducing the inflammation. The cerebral spinal fluid (CSF) findings include lymphocytic meningitis with a mild increase in protein. The CSF glucose is usually normal but can be low. Certain areas of the nervous system are more commonly affected in neurosarcoidosis. These include cranial nerve involvement, basilar meningitis, myelopathy, and anterior hypothalamic disease with associated diabetes insipidus. Seizures and cognitive changes also occur. Of the cranial nerves, seventh nerve paralysis can be transient and mistaken for Bell's palsy (idiopathic seventh nerve paralysis). Since this form of neurosarcoidosis often resolves within weeks and may not recur, it may have occurred prior to a definitive diagnosis of sarcoidosis. Optic neuritis is another cranial nerve manifestation of sarcoidosis. This manifestation is more chronic and usually requires long-term systemic therapy. It can be associated with both anterior and posterior uveitis. Differentiating between neurosarcoidosis and multiple sclerosis can be difficult at times. Optic neuritis can occur in both diseases. In some patients with sarcoidosis, multiple enhancing white matter abnormalities may be detected by MRI, suggesting multiple sclerosis. In such cases, the presence of meningeal enhancement or hypothalamic involvement suggests neurosarcoidosis, as does evidence of extraneurologic disease such as pulmonary or skin involvement, which also suggests sarcoidosis. Since the response of neurosarcoidosis to glucocorticoids and cytotoxic therapy is different from that of multiple sclerosis, differentiating between these disease entities is important.

CARDIAC

The presence of cardiac involvement is influenced by race. Over a quarter of Japanese sarcoidosis patients develop cardiac disease, whereas only 5% of sarcoidosis patients in the United States and Europe develop cardiac disease. However, there is no apparent difference between whites and African Americans. Cardiac disease usually presents as either congestive heart failure or cardiac arrhythmias. Both manifestations result from infiltration of the heart muscle by granulomas. Diffuse granulomatous involvement of the heart muscle can lead to ejection fractions below 10%. Even in this situation, improvement in the ejection fraction can occur with systemic therapy. Arrhythmias can also occur with diffuse infiltration or with more patchy cardiac involvement. If the atrioventricular (AV) node is infiltrated, heart block can occur. This can be detected by routine electrocardiography. Ventricular arrhythmias and sudden death due to ventricular tachycardia are common causes of death. Arrhythmias are best detected using 24-h ambulatory monitoring. Because ventricular arrhythmias are usually multifocal due to patchy multiple granulomas in the heart, ablation therapy is not useful. Patients with significant ventricular arrhythmias should be considered for an implanted defibrillator, which appears to have reduced the rate of death in cardiac sarcoidosis. While systemic therapy can be useful in treating the arrhythmias, patients may still have

malignant arrhythmias up to 6 months after starting successful treatment, and the risk for recurrent arrhythmias occurs whenever medications are tapered.

MUSCULOSKELETAL SYSTEM

Direct granulomatous bone and muscle involvement as documented by x-ray, MRI **(Fig. 14-7)**, gallium scan, or biopsy can be seen in about 10% of sarcoidosis patients. However, a larger percentage of sarcoidosis patients complain of myalgias and arthralgias. These complaints are similar to those reported by patients with other inflammatory diseases, including chronic infections such as mononucleosis. Fatigue associated with sarcoidosis may be overwhelming for many patients. Recent studies have demonstrated a link between fatigue and small peripheral nerve fiber disease in sarcoidosis.

OTHER ORGAN INVOLVEMENT

Although sarcoidosis can affect any organ of the body, rarely does it involve the breast, testes, ovary, or stomach. Because of the rarity of involvement, a mass in one of these areas requires a biopsy to rule out other diseases including cancer. For example, in a study of breast problems in female sarcoidosis patients, a breast lesion was more likely to be granulomas from sarcoidosis than from breast cancer. However, findings on the physical examination or mammogram cannot reliably differentiate between these lesions. More importantly, as women with sarcoidosis age, breast cancer becomes more common. Therefore, it is recommended that routine screening including mammography be performed along with other imaging studies (ultrasound, MRI) or biopsy as clinically indicated.

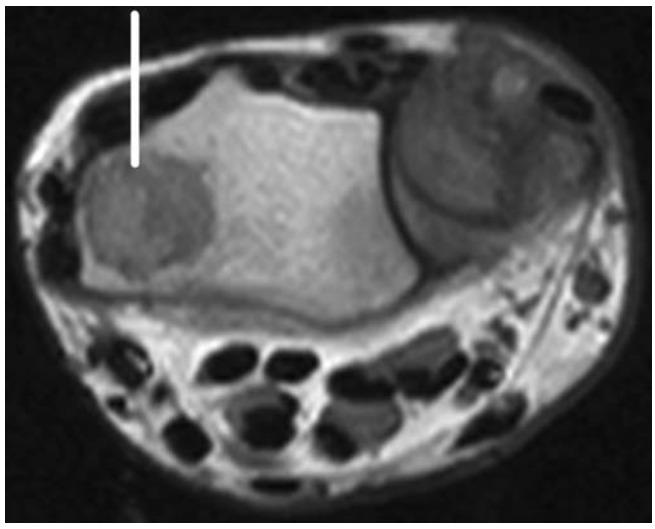


FIGURE 14-7
MRI of wrist demonstrating large cyst in a sarcoidosis patient (*line*).

COMPLICATIONS

Sarcoidosis is usually a self-limited, non-life-threatening disease. However, organ-threatening disease can occur. These complications can include blindness, paraplegia, or renal failure. Death from sarcoidosis occurs in about 5% of patients seen in sarcoidosis referral clinics. The usual causes of death related to sarcoidosis are from lung, cardiac, neurologic, or liver involvement. In respiratory failure, an elevation of the right atrial pressure is a poor prognostic finding. Lung complications can also include infections such as mycetoma, which can subsequently lead to massive bleeding. In addition, the use of immunosuppressive agents can increase the incidence of serious infections.

LABORATORY FINDINGS

The chest roentgenogram remains the most commonly used tool to assess lung involvement in sarcoidosis. As noted above, the chest roentgenogram classifies involvement into four stages, with stages 1 and 2 having hilar and paratracheal adenopathy. The CT scan has been used increasingly in evaluating interstitial lung disease. In sarcoidosis, the presence of adenopathy and a nodular infiltrate is not specific for sarcoidosis. Adenopathy up to 2 cm can be seen in other inflammatory lung diseases such as idiopathic pulmonary fibrosis. However, adenopathy >2 cm in the short axis supports the diagnosis of sarcoidosis over other interstitial lung diseases.

The positive emission tomography (PET) scan has increasingly replaced gallium 67 scanning to identify areas of sarcoidosis in the chest and other parts of the body. Both tests can be used to identify potential areas for biopsy. Cardiac PET scanning has also proved useful in assessing cardiac sarcoidosis. A positive PET scan may be due to the granulomas from sarcoidosis and not to disseminated malignancy.

Serum levels of angiotensin-converting enzyme (ACE) can be helpful in the diagnosis of sarcoidosis. However, the test has somewhat low sensitivity and specificity. Elevated levels of ACE are reported in 60% of patients with acute disease and only 20% of patients with chronic disease. Although there are several causes for mild elevation of ACE, including diabetes, elevations of >50% of the upper limit of normal are seen in only a few conditions including sarcoidosis, leprosy, Gaucher's disease, hyperthyroidism, and disseminated granulomatous infections such as miliary tuberculosis. There is an insertion/deletion (I/D) polymorphism of the *ACE* gene on what is felt to be in the noncritical

part of the gene. There is a phenotypic difference for ACE levels, with II polymorphism having the lowest and DD polymorphism the highest levels of ACE for both sarcoidosis patients and healthy controls. There is no clear-cut association between ACE phenotype and clinical manifestation of disease. Because the ACE level is determined by a biologic assay, the concurrent use of an ACE inhibitor such as lisinopril will lead to a very low ACE level.

DIAGNOSIS

The diagnosis of sarcoidosis requires both compatible clinical features and pathologic findings. Since the cause of sarcoidosis remains elusive, the diagnosis cannot be made with 100% certainty. Nevertheless, the diagnosis can be made with reasonable certainty based on history and physical features along with laboratory and pathologic findings.

Patients are usually evaluated for possible sarcoidosis based on two scenarios **(Fig. 14-8)**. In the first scenario, a patient may undergo a biopsy revealing a noncaseating granuloma in either a pulmonary or an extrapulmonary organ. If the clinical presentation is consistent with sarcoidosis and there is no alternative cause for the granulomas identified, then the patient is felt to have sarcoidosis.

In the second scenario, signs or symptoms suggesting sarcoidosis such as the presence of bilateral adenopathy may be present in an otherwise asymptomatic patient or a patient with uveitis or a rash consistent with sarcoidosis. At this point, a diagnostic procedure should be performed. For the patient with a compatible skin lesion, a skin biopsy should be considered. Other biopsies to consider could include liver, extrathoracic lymph node, or muscle. In some cases, a biopsy of the affected organ may not be easy to perform (such as a brain or spinal cord lesion). In other cases, such as an endomyocardial biopsy, the likelihood of a positive biopsy is low. Because of the high rate of pulmonary involvement in these cases, the lung may be easier to approach by bronchoscopy. During the bronchoscopy, a transbronchial biopsy, bronchial biopsy, or transbronchial needle aspirate of an enlarged mediastinal lymph node can be performed. The endobronchial ultrasonography-guided transbronchial needle aspirate may be particularly useful in the patient with stage 1 disease (i.e., adenopathy without infiltrates).

If the biopsy reveals granulomas, an alternative diagnosis such as infection or malignancy must be excluded. Bronchoscopic washings can be sent for cultures for fungi and tuberculosis. For the pathologist, the more tissue that is provided, the more comfortable is the diagnosis of sarcoidosis. A needle aspirate may be adequate in an otherwise classic case of sarcoidosis, but may be insufficient in a patient in whom lymphoma or fungal infection is a likely alternative diagnosis. Since granulomas can be seen on the edge of a lymphoma, the presence of a few granulomas from a needle aspirate

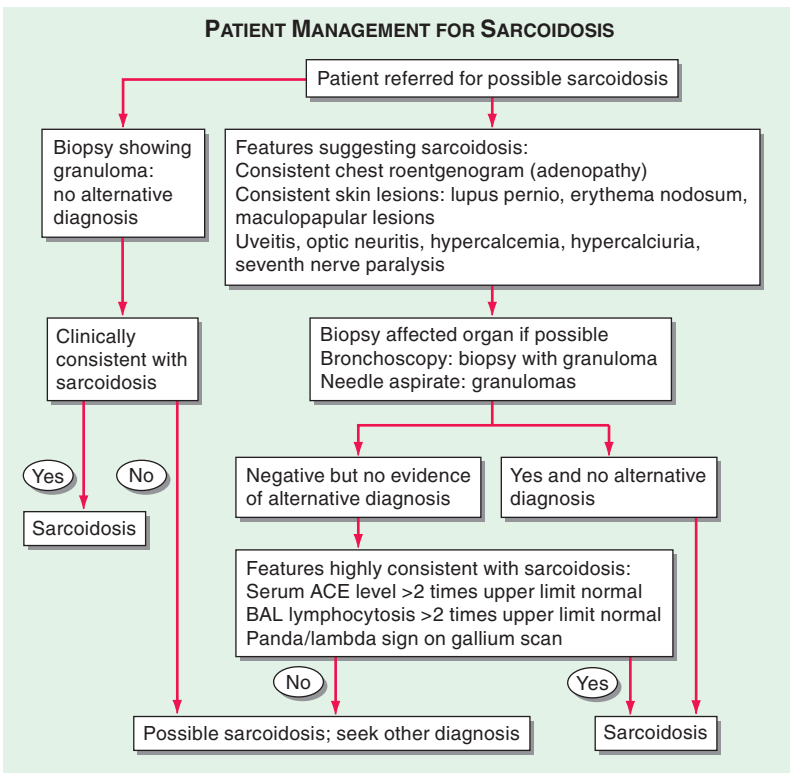


FIGURE 14-8
Proposed approach to management of patient with possible sarcoidosis. Presence of one or more of these features supports the diagnosis of sarcoidosis: uveitis, optic neuritis, hypercalcemia, hypercalciuria, seventh cranial nerve paralysis, diabetes insipidus.

may not be sufficient to clarify the diagnosis. Mediastinoscopy remains the procedure of choice to confirm the presence or absence of lymphoma in the mediastinum. Alternatively, for most patients, evidence of extrathoracic disease (e.g., eye involvement) may further support the diagnosis of sarcoidosis.

For patients with negative pathology, positive supportive tests may increase the likelihood of the diagnosis of sarcoidosis. These tests include an elevated ACE level, which can also be elevated in other granulomatous diseases but not in malignancy. A positive gallium scan can support the diagnosis if increased activity is noted in the parotids and lacrimal glands (*panda sign*) or in the right paratracheal and left hilar area (*lambda sign*). A BAL is often performed during the bronchoscopy. An increase in the percentage of lymphocytes supports the diagnosis of sarcoidosis. The use of the lymphocyte markers CD4 and CD8 can be used to determine the CD4/CD8 ratio of these increased lymphocytes in the BAL fluid. A ratio of >3.5 is strongly supportive of sarcoidosis but is less sensitive than an increase in lymphocytes alone. Although in general, an increase in BAL lymphocytes is supportive of the diagnosis, other conditions must be considered.

These supportive tests when combined with commonly associated clinical features of the disease, which are not diagnostic of sarcoidosis, can enhance the diagnostic probability. These nondiagnostic features include uveitis, renal stones, hypercalcemia, seventh cranial nerve paralysis, or erythema nodosum.

The *Kviem-Siltzbach procedure* is a specific diagnostic test for sarcoidosis. An intradermal injection of specially prepared tissue derived from the spleen of a known sarcoidosis patient is biopsied 4–6 weeks after injection. If noncaseating granulomas are seen, this is highly specific for the diagnosis of sarcoidosis. Unfortunately, there is no commercially available Kviem-Siltzbach reagent, and some locally prepared batches have lower specificity. Thus, this test is of historic interest and is rarely used in current clinical practice.

Because the diagnosis of sarcoidosis can never be certain, over time other features may arise that lead to an alternative diagnosis. Conversely, evidence for new organ involvement may eventually confirm the diagnosis of sarcoidosis.

PROGNOSIS

The risk of death or loss of organ function remains low in sarcoidosis. Poor outcomes usually occur in patients who present with advanced disease in whom treatment seems to have little impact. In these cases, irreversible fibrotic changes have frequently occurred.

For the majority of patients, initial presentation occurs during the granulomatous phase of the disease as depicted in Fig. 14-1. It is clear that many patients resolve their disease within 2–5 years. These patients are felt to have acute, self-limiting sarcoidosis. However, there is a form of the disease that does not resolve within the first 2–5 years. These chronic patients can be identified at presentation by certain risk factors at presentation such as fibrosis on chest roentgenogram, presence of lupus pernio, bone cysts, cardiac or neurologic disease (except isolated seventh nerve paralysis), and presence of renal calculi due to hypercalciuria. Recent studies also indicate that patients who require glucocorticoids for any manifestation of their disease in the first 6 months of presentation have a >50% chance of having chronic disease. In contrast, <10% of patients who require no systemic therapy in the first 6 months will require chronic therapy.

TREATMENT Sarcoidosis

The indications for therapy should be based on symptoms. The patient with elevated liver function tests or an abnormal chest roentgenogram probably does not benefit from treatment. However, these patients should be monitored for evidence of progressive, symptomatic disease.

One approach to therapy is summarized in Figs. 14-9 and 14-10. We have divided the approach into treating acute versus chronic disease. For acute disease, no therapy remains a viable option for patients with no or mild symptoms. For symptoms confined to only one organ, topical therapy is preferable. For multiorgan disease or disease too extensive for topical therapy, an approach to systemic therapy is outlined. Glucocorticoids remain the drugs of choice for this disease. However, the decision to continue to treat with glucocorticoids or to add steroid-sparing agents depends on the tolerability, duration, and dosage of glucocorticoids. Table 14-2 summarizes the dosage and monitoring of several commonly used drugs. According to the available trials, evidence-based recommendations are made. Most of these recommendations are for pulmonary disease because most of the trials were performed only in pulmonary disease. Treatment recommendations for extrapulmonary disease are usually similar with a few modifications. For example, the dosage of glucocorticoids is usually higher for neurosarcoidosis and lower for cutaneous disease. There was some suggestion that higher doses would be beneficial for cardiac sarcoidosis, but one study found that initial doses >40 mg/d prednisone were associated with a worse outcome because of toxicity.

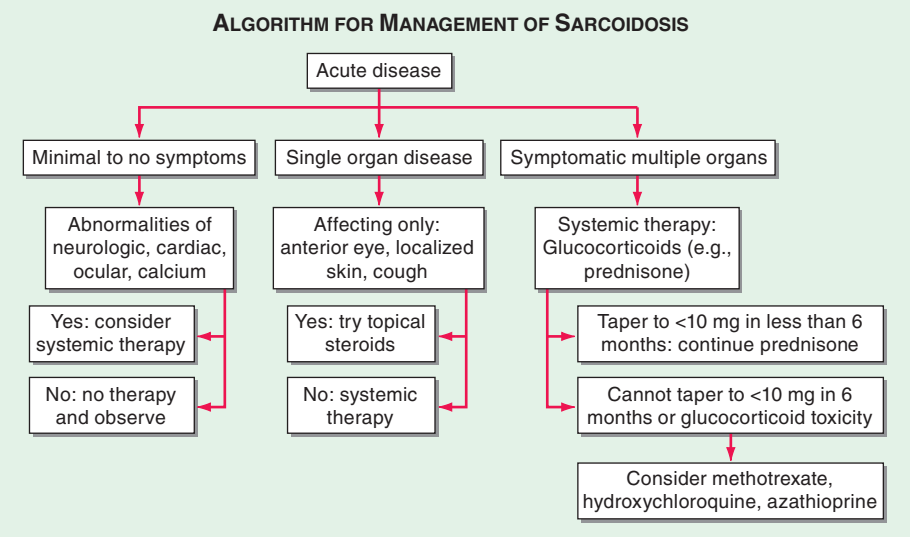


FIGURE 14-9
The management of acute sarcoidosis is based on level of symptoms and extent of organ involvement. In patients with mild symptoms, no therapy may be needed unless specified manifestations are noted.

While most patients receive glucocorticoids as their initial systemic therapy, toxicity associated with prolonged therapy often leads to steroid-sparing alternatives. The antimalarial drugs such as hydroxychloroquine are more effective for skin than pulmonary disease. Minocycline may also be useful for cutaneous sarcoidosis. For pulmonary and other extra-pulmonary disease, cytotoxic agents are often employed. These include methotrexate, azathioprine, chlorambucil, and cyclophosphamide. The most widely studied cytotoxic agent has been methotrexate. This agent works in approximately two-thirds of sarcoidosis patients, regardless of the disease manifestation. As noted in Table 14-2, specific guidelines for monitoring therapy have been recommended. Cytokine modulators such as thalidomide and pentoxifylline have also been used in a limited number of cases.

The anti-TNF agents have recently been studied in sarcoidosis, with prospective randomized trials of both etanercept and infliximab completed. Etanercept has a limited role as a steroid-sparing agent. Conversely, infliximab significantly improved lung function when given to

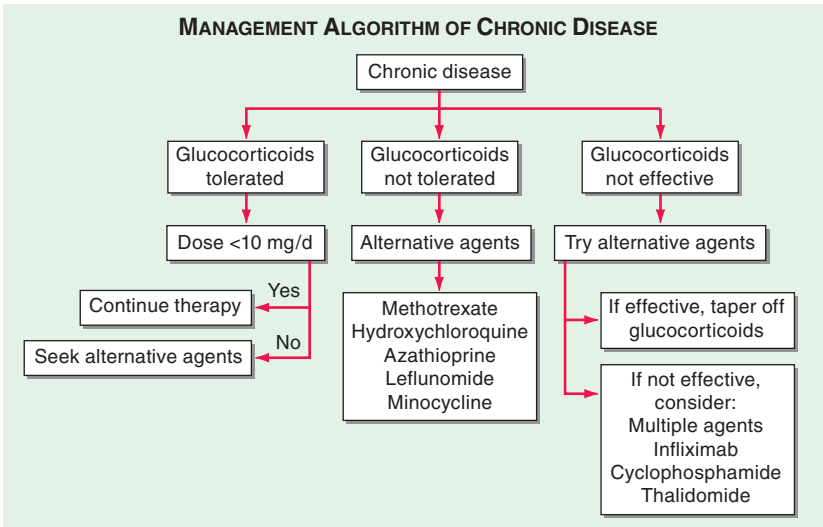


FIGURE 14-10
Approach to chronic disease is based on whether glucocorticoid therapy is tolerated or not.

TABLE 14-2

COMMONLY USED DRUGS TO TREAT SARCOIDOSIS

DRUG	INITIAL DOSE	MAINTENANCE DOSE	MONITORING	TOXICITY	SUPPORT THERAPY[a]	SUPPORT MONITORING[a]
Prednisone	20–40 mg qd	Taper to 5–10 mg	Glucose, blood pressure, bone density	Diabetes, osteoporosis	A: Acute pulmonary D: Extrapulmonary	
Hydroxychloroquine	200–400 mg qd	400 mg qd	Eye exam q6–12 mo	Ocular	B: Some forms of disease	D: Routine eye exam
Methotrexate	10 mg qw	2.5–15 mg qw	CBC, renal, hepatic q2mo	Hematologic, nausea, hepatic, pulmonary	B: Steroid sparing C: Some forms chronic disease	D: Routine hematologic, renal, and hepatic monitoring
Azathioprine	50–150 mg qd	50–200 mg qd	CBC, renal q2mo	Hematologic, nausea	C: Some forms chronic disease	D: Routine hematologic monitoring
Infliximab	3–5 mg/kg q2wk for 2 doses	3–10 mg/kg q4–8 wk	Initial PPD	Infections, allergic reaction, carcinogen	A: Chronic pulmonary disease	B: Caution in patients with latent tuberculosis or advanced congestive heart failure

[a]Grade A: supported by at least two double-blind randomized control trials; grade B: supported by prospective cohort studies; grade C: supported primarily by two or more retrospective studies; grade D: only one retrospective study or based on experience in other diseases.
Abbreviations: CBC, complete blood count; PPD, purified protein derivative test for tuberculosis.
Source: Adapted from RP Baughman and O Selroos: Evidence-based approach to treatment of sarcoidosis, in PG Gibson et al (eds): *Evidence-Based Respiratory Medicine*. Oxford, BMJ Books Blackwell, 2005, pp 491-508.

patients with chronic disease already on glucocorticoids and cytotoxic agents. The difference in response for these two agents is similar to that observed in Crohn's disease, where infliximab is effective and etanercept is not. In addition, there is a higher risk for reactivation of tuberculosis with infliximab compared to etanercept. The differential response rate could be explained by differences in mechanism of action since etanercept is a TNF receptor antagonist and infliximab is a monoclonal antibody against TNF. In contrast to etanercept, infliximab also binds to TNF on the surface of some cells that are releasing TNF and this can lead to cell lysis. This effect has been documented in Crohn's disease. There is currently limited information about the dose and effectiveness of adalimumab, another anti-TNF antibody, versus infliximab in sarcoidosis. The role of the newer therapeutic agents for sarcoidosis is still evolving. However, these targeted therapies confirm that TNF may be an important target, especially in the treatment of chronic disease. However, these agents are not a panacea, since sarcoidosis-like disease has occurred in patients treated with anti-TNF agents for non-sarcoidosis indications.

CHAPTER 15

FAMILIAL MEDITERRANEAN FEVER AND OTHER HEREDITARY RECURRENT FEVERS

Daniel L. Kastner

Familial Mediterranean fever (FMF) is the prototype of a group of inherited diseases **(Table 15-1)** that are characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation and, in some individuals, the eventual development of systemic AA amyloidosis (Chap. 16). Because of the relative infrequency of high-titer autoantibodies or antigen-specific T cells, the term *autoinflammatory* has been proposed to describe these disorders, rather than autoimmune. The innate immune system, with its myeloid effector cells and germline receptors for pathogen-associated molecular patterns and endogenous danger signals, plays a predominant role in the pathogenesis of the autoinflammatory diseases.

BACKGROUND AND PATHOPHYSIOLOGY

FMF was first recognized among Armenians, Arabs, Turks, and non-Ashkenazi (primarily North African and Iraqi) Jews. With the advent of genetic testing, FMF has been documented with increasing frequency among Ashkenazi Jews, Italians, and other Mediterranean populations, and occasional cases have been confirmed even in the absence of known Mediterranean ancestry. FMF is recessively inherited, but, particularly in countries where families are small, a positive family history can only be elicited in ~50% of cases. DNA testing demonstrates carrier frequencies as high as 1:3 among affected populations, suggesting a heterozygote advantage.

The FMF gene encodes a 781-amino acid, ~95 kDa protein denoted *pyrin* (or *marenostrin*) that is expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts. The N-terminal 92 amino acids of pyrin define a motif, the PYRIN domain, that is similar in structure to death domains, death effector domains, and caspase recruitment domains. PYRIN domains mediate homotypic protein-protein interactions and have been found in several other proteins, including cryopyrin, which is mutated in three other recurrent fever syndromes. Through a number of mechanisms, including the interaction of the PYRIN domain with an intermediary adaptor protein, pyrin regulates caspase-1 (interleukin [IL] 1β-converting enzyme), and thereby IL-1β secretion. Mice bearing FMF-associated pyrin mutations exhibit inflammation and excessive IL-1 production.

ACUTE ATTACKS

Febrile episodes in FMF may begin even in early infancy; 90% of patients have had their first attack by age 20. Typical FMF episodes generally last 24–72 hours, with arthritic attacks tending to last somewhat longer. In some patients the episodes occur with great regularity, but more often the frequency of attacks varies over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients relate them to physical exertion, emotional stress, or menses; pregnancy may be associated with remission.

If measured, fever is nearly always present throughout FMF attacks. Severe hyperpyrexia and even febrile seizures may be seen in infants, and fever is sometimes the only manifestation of FMF in young children.

Over 90% of FMF patients experience abdominal attacks at some time. Episodes range in severity from dull, aching pain and distention with mild tenderness on direct palpation to severe generalized pain with absent bowel sounds, rigidity, rebound tenderness, and air-fluid levels on upright radiographs. CT scanning may demonstrate a small amount of fluid in the abdominal

TABLE 15-1

THE HEREDITARY RECURRENT FEVER SYNDROMES

	FMF	TRAPS	HIDS	MWS	FCAS	NOMID
Ethnicity	Jewish, Arab, Turkish, Armenian, Italian	Any ethnic group	Predominantly Dutch, northern European	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	Recessive[a]	Dominant	Recessive	Dominant	Dominant	Usually de novo mutations
Gene/ chromosome	*MEFV*/16p13.3	*TNFRSF1A*/12p13	*MVK*/12q24	*NLRP3*/1q44	*NLRP3*/1q44	*NLRP3*/1q44
Protein	Pyrin	p55 TNF receptor	Mevalonate kinase	Cryopyrin	Cryopyrin	Cryopyrin
Attack length	1–3 days	Often > 7 days	3–7 days	1–2 days	Minutes–3 days	Continuous, with flares
Serosa	Pleurisy, peritonitis; asymptomatic pericardial effusions	Pleurisy, peritonitis, pericarditis	Abd pain, but seldom peritonitis; pleurisy, pericarditis uncommon	Abd pain common; pleurisy, pericarditis rare	Rare	Rare
Skin	Erysipeloid erythema	Centrifugally migrating erythema	Diffuse maculopapular rash; oral ulcers	Diffuse urticaria-like rash	Cold-induced urticaria-like rash	Diffuse urticaria-like rash
Joints	Acute monoarthritis; chronic hip arthritis (rare)	Acute monoarthritis, arthralgia	Arthralgia, oligoarthritis	Arthralgia, large joint oligoarthritis	Polyarthralgia	Epiphyseal, patellar overgrowth, clubbing
Muscle	Exercise-induced myalgia common; protracted febrile myalgia rare	Migratory myalgia	Uncommon	Myalgia common	Sometimes myalgia	Sometimes myalgia
Eyes, ears	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Uncommon	Conjunctivitis, episcleritis, optic disc edema; sensorineural hearing loss	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness, sensorineural hearing loss
CNS	Aseptic meningitis rare	Headache	Headache	Headache	Headache	Aseptic meningitis, seizures
Amyloidosis	Most common in M694V homozygotes	~15% of cases	Uncommon	~25% of cases	Uncommon	Late complication
Treatment	Oral colchicine prophylaxis Rilonacept in colchicine-resistant or -intolerant patients	Glucocorticoids, etanercept, anakinra (IL-1 receptor antagonist)	NSAIDs for fever; IL-1β and TNF inhibitors investigational	Anakinra, rilonacept, canakinumab	Anakinra, rilonacept, canakinumab	Anakinra

[a]A substantial percentage of patients with clinical FMF have only a single demonstrable *MEFV* mutation on DNA sequencing.

Abbreviations: FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAIDs, nonsteroidal anti-inflammatories; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

cavity. If such patients undergo exploratory laparotomy, a sterile, neutrophil-rich peritoneal exudate is present, sometimes with adhesions from previous episodes. Ascites is rare.

Pleural attacks are usually manifested by unilateral, sharp, stabbing chest pain. Radiographs may show atelectasis and sometimes an effusion. If performed, thoracentesis demonstrates an exudative fluid rich in neutrophils. After repeated attacks, pleural thickening may develop.

FMF arthritis is most frequent among individuals homozygous for the M694V mutation, which is especially common in the non-Ashkenazi Jewish population. Acute arthritis in FMF is usually monoarticular, affecting the knee, ankle, or hip, although other patterns can be seen, particularly in children. Large sterile effusions rich in neutrophils are frequent, without commensurate erythema or warmth. Even after repeated arthritic attacks, radiographic changes are rare. Before the advent of colchicine prophylaxis, chronic arthritis of the knee or hip were seen in ~5% of FMF patients with arthritis. Chronic sacroiliitis can occur in FMF irrespective of the HLA-B27 antigen, even in the face of colchicine therapy. In the United States, FMF patients are much more likely to have arthralgia than arthritis.

The most characteristic cutaneous manifestation of FMF is erysipelas-like erythema, a raised erythematous rash that most commonly occurs on the dorsum of the foot, ankle, or lower leg alone or in combination with abdominal pain, pleurisy, or arthritis. Biopsy demonstrates perivascular infiltrates of granulocytes and monocytes. This rash is seen most often in M694V homozygotes and is relatively rare in the United States.

Exercise-induced (nonfebrile) myalgia is common in FMF, and a small percentage of patients develop a protracted febrile myalgia that can last several weeks. Symptomatic pericardial disease is rare, although some patients have small pericardial effusions as an incidental echocardiographic finding. Unilateral acute scrotal inflammation may occur in prepubertal boys. Aseptic meningitis has been reported in FMF, but the causal connection is controversial. Vasculitis, including Henoch-Schönlein purpura and polyarteritis nodosum (Chap. 11) may be seen at increased frequency in FMF.

Laboratory features of FMF attacks are consistent with acute inflammation and include an elevated erythrocyte sedimentation rate, leukocytosis, thrombocytosis (in children), and elevations in C-reactive protein, fibrinogen, haptoglobin, and serum immunoglobulins. Transient albuminuria and hematuria may also be seen.

AMYLOIDOSIS

Before the advent of colchicine prophylaxis, systemic amyloidosis was a common complication of FMF. It is caused by deposition of a fragment of serum amyloid A, an acute-phase reactant, in the kidneys, adrenals, intestine, spleen, lung, and testes (Chap. 16). Amyloidosis should be suspected in patients who have proteinuria between attacks; renal or rectal biopsy are used most often to establish the diagnosis. Risk factors include the M694V homozygous genotype, positive family history (independent of FMF mutational status), the SAA 1 genotype, male gender, noncompliance with colchicine therapy, and having grown up in the Middle East.

DIAGNOSIS

For typical cases, physicians experienced with FMF can often make the diagnosis on clinical grounds alone. Clinical criteria sets for FMF have been shown to have high sensitivity and specificity in parts of the world where the pretest probability of FMF is high. Genetic testing can provide a useful adjunct in ambiguous cases or for physicians not experienced in FMF. Most of the more severe disease-associated FMF mutations are in exon 10 of the gene, with a smaller group of milder variants in exon 2. An updated list of mutations for FMF and other hereditary recurrent fevers can be found online at *http://fmf.igh.cnrs.fr/infevers/*.

Genetic testing has permitted a broadening of the clinical spectrum and geographic distribution of FMF and may be of prognostic value. Most studies indicate that M694V homozygotes have an earlier age of onset and a higher frequency of arthritis, rash, and amyloidosis. In contrast, the E148Q variant is usually associated with milder disease. E148Q is sometimes found in *cis* with exon 10 mutations, which complicates the interpretation of genetic test results. Only ~70% of patients with clinically typical FMF have two identifiable mutations in *trans*, suggesting either that current screening methods do not detect all of the relevant mutations or that one mutation may be sufficient to cause disease under some circumstances. In these cases clinical judgment is very important, and sometimes a therapeutic trial of colchicine may help to confirm the diagnosis. Genetic testing of unaffected individuals is usually inadvisable, because of the possibility of nonpenetrance and the potential impact of a positive test on future insurability.

If a patient is seen during his or her first attack, the differential diagnosis may be broad, although delimited by the specific organ involvement. After several attacks the differential diagnosis may include the other hereditary recurrent fever syndromes (Table 15-1); the syndrome of periodic fever with aphthous ulcers, pharyngitis, and cervical adenopathy (PFAPA); systemic-onset juvenile rheumatoid arthritis or adult Still's disease; porphyria; hereditary angioedema; inflammatory bowel disease; and, in women, gynecologic disorders.

TREATMENT **Familial Mediterranean Fever**

The treatment of choice for FMF is daily oral colchicine, which decreases the frequency and intensity of attacks and prevents the development of amyloidosis in compliant patients. Intermittent dosing at the onset of attacks is not as effective as daily prophylaxis and is of unproven value in preventing amyloidosis. The usual adult dose of colchicine is 1.2–1.8 mg/d, which causes substantial reduction in symptoms in two-thirds of patients and some improvement in >90%. Children may require lower doses, although not proportionately to body weight.

Common side effects of colchicine include bloating, abdominal cramps, lactose intolerance, and diarrhea. They can be minimized by starting at a low dose and gradually advancing as tolerated, splitting the dose, use of simethecone for flatulence, and avoidance of dairy products. If taken by either parent at the time of conception, colchicine may cause a small increase in the risk of trisomy 21 (Down syndrome). In elderly patients with renal insufficiency, colchicine can cause a myoneuropathy characterized by proximal muscle weakness and elevation of the creatine kinase. Cyclosporine inhibits hepatic excretion of colchicine by its effects on the MDR-1 transport system, sometimes leading to colchicine toxicity in patients who have undergone renal transplantation for amyloidosis. Intravenous colchicine should generally not be administered to patients already taking oral colchicine, because severe, sometimes fatal, toxicity can occur in this setting.

A recent study found that the IL-1 receptor antagonist rilonacept reduces the frequency of attacks and seems to be a treatment option for patients with colchicine-resistant or -intolerant FMF. Bone marrow transplantation has been suggested for refractory FMF, but the risk-benefit ratio is currently regarded as unacceptable.

OTHER HEREDITARY RECURRENT FEVERS

Within 5 years of the discovery of the FMF gene, three additional genes causing five other hereditary recurrent fever syndromes were identified, catalyzing a paradigm shift in diagnosis and treatment of these disorders.

TNF RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)

TRAPS is caused by dominantly inherited mutations in the extracellular domains of the 55-kDa TNF receptor (TNFRSF1A, p55). Although originally described in a large Irish family (and hence the name *familial Hibernian fever*), TRAPS has a broad ethnic distribution. TRAPS episodes often begin in childhood. The duration of attacks ranges from 1–2 days to as long as several weeks, and in severe cases symptoms may be nearly continuous. In addition to peritoneal, pleural, and synovial attacks similar to FMF, TRAPS patients frequently have ocular inflammation (most often conjunctivitis and/or periorbital edema), and a distinctive migratory myalgia with overlying painful erythema may be present. TRAPS patients generally respond better to glucocorticoids than to prophylactic colchicine. About 15% develop amyloidosis. The diagnosis of TRAPS is based on the demonstration of *TNFRSF1A* mutations in the presence of characteristic symptoms. Leukocytes from patients with certain TRAPS mutations exhibit a defect in TNF receptor-shedding, possibly impairing normal homeostasis. However, a more complex picture is emerging, with a number of functional abnormalities, some of which are ligand-independent, contributing to the autoinflammatory phenotype. Etanercept, a TNF inhibitor, ameliorates TRAPS attacks, although its effect on amyloidosis is unproven. Perhaps because of the ligand-independent signaling abnormalities in TRAPS, IL-1 inhibition has been beneficial in some patients.

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (HIDS)

HIDS is a recessively inherited recurrent fever syndrome found primarily in individuals of northern European ancestry. It is caused by mutations in mevalonate kinase (*MVK*), encoding an enzyme involved in the synthesis of cholesterol and nonsterol isoprenoids. Attacks usually begin in infancy, and last 3–5 days. Clinically distinctive features include painful cervical adenopathy, a diffuse maculopapular rash sometimes affecting the palms and soles, and aphthous ulcers; pleurisy is rare, as is amyloidosis. Although originally defined by the persistent elevation of serum IgD, disease activity is not related to IgD levels, and some patients with FMF or TRAPS may have modestly increased serum IgD. Moreover, occasional patients with *MVK* mutations and recurrent fever have normal IgD levels. All patients with mutations have markedly elevated urinary mevalonate levels during their febrile attacks, although the inflammatory manifestations are likely to be due to a deficiency of isoprenoids rather than an excess of mevalonate. There is currently no established treatment for HIDS, although intermittent or continuous IL-1 inhibition are investigational.

THE CRYOPYRINOPATHIES, OR CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS)

Three hereditary febrile syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome

(MWS), and neonatal-onset multisystem inflammatory disease (NOMID), are all caused by mutations in *NLRP3* (formerly known as *CIAS1)*, the gene encoding cryopyrin (or NLRP3), and represent a clinical spectrum of disease. FCAS patients develop chills, fever, headache, arthralgia, conjunctivitis, and an urticaria-like rash in response to generalized cold exposure. In MWS, an urticarial rash is noted, but it is not usually induced by cold; MWS patients also develop fevers, abdominal pain, limb pain, arthritis, conjunctivitis, and, over time, sensorineural hearing loss. NOMID is the most severe of the three disorders, with chronic aseptic meningitis, a characteristic arthropathy, and rash. Like the FMF protein, pyrin, cryopyrin has an N-terminal PYRIN domain. Cryopyrin regulates IL-1β production through the formation of a macromolecular complex termed the *inflammasome*. Peripheral blood leukocytes from patients with FCAS, MWS, and NOMID release increased amounts of IL-1β upon in vitro stimulation, relative to healthy controls. Macrophages from cryopyrin-deficient mice exhibit decreased IL-1β production in response to certain gram-positive bacteria, bacterial RNA, and monosodium urate crystals. Patients with all three cryopyrino-pathies show a dramatic response to injections of IL-1 inhibitors. Increased IL-1 signaling is also a feature of the recently-described deficiency in the interleukin-1 receptor antagonist (DIRA), a recessively inherited disorder similarly responsive to anakinra treatment. In contrast to the cryopyrinopathies, DIRA presents with pustular skin lesions and multifocal sterile osteomyelitis, and fever is often not a prominent feature.

CHAPTER 16

AMYLOIDOSIS

David C. Seldin ■ Martha Skinner

GENERAL PRINCIPLES

Amyloidosis is the term for diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. These diseases are a subset of a growing group of disorders attributed to misfolding of proteins. Among these are Alzheimer's disease and other neurodegenerative diseases, transmissible prion diseases, and genetic diseases caused by mutations that lead to misfolding, aggregation, and protein loss of function, such as certain of the cystic fibrosis mutations. Amyloid fibrils share a common β-pleated sheet structural conformation that confers unique staining properties. The term *amyloid* was coined by the pathologist Rudolf Virchow around 1854, who thought such deposits were cellulose-like under the microscope.

Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits and are classified according to whether they are systemic or localized, acquired or inherited, and by their clinical patterns **(Table 16-1)**. The accepted nomenclature is *AX*, where *A* indicates amyloidosis and *X* represents the protein in the fibril. *AL* is amyloid composed of immunoglobulin light chains (LCs), and has been called *primary systemic amyloidosis*; it arises from a clonal B cell disorder and may be associated with myeloma or lymphoma. *AF* groups the *familial amyloidoses*, most commonly due to mutations in transthyretin, the transport protein for thyroid hormone and retinol-binding protein. *AA* amyloid is composed of the acute-phase reactant serum amyloid A protein and occurs in the setting of chronic inflammatory or infectious diseases and has been termed *secondary amyloidosis*. $A\beta_2M$ is amyloid composed of β_2-microglobulin and occurs in individuals with end-stage renal disease (ESRD) of long duration. *A*β is the most common form of localized amyloidosis. *A*β is deposited in the brain in Alzheimer's disease and is derived from abnormal proteolytic processing of the amyloid precursor protein (APP).

Diagnosis and treatment of the amyloidoses rest upon the pathologic diagnosis of amyloid deposits and immunohistochemical or biochemical identification of amyloid type **(Fig. 16-1)**. In the systemic amyloidoses, the involved organs can be biopsied, but amyloid deposits may be found in any tissue of the body. Historically, blood vessels of the gingiva or rectal mucosa were examined, but the most easily accessible tissue, positive in more than 80% of patients with systemic amyloidosis, is fat. After local anesthesia, needle aspiration of fat from the abdominal wall can be expelled onto a slide and stained, avoiding even a minor surgical procedure. If this material is negative, biopsy of kidney, heart, liver, or gastrointestinal tract can be considered. The regular β-sheet structure of amyloid deposits exhibits a unique green birefringence by polarized light microscopy when stained with Congo red dye; the 10-nm-diameter fibrils can be seen directly by electron microscopy of paraformaldehyde-fixed tissue. Once amyloid is found, the protein type must be determined, usually by immunohistochemistry, immunoelectron microscopy, or by extraction and biochemical analysis by mass spectrometry or other technique. Careful evaluation of the patient's history, physical findings, and clinical presentation, including age and ethnic origin, organ system involvement, underlying diseases, and family history, can provide helpful clues to the type of amyloid.

The mechanisms of fibril formation and tissue toxicity remain controversial. Factors that contribute to fibrillogenesis include variant or unstable protein structure, extensive β-sheet conformation of the precursor protein, proteolytic processing of the precursor protein, association with components of the serum or extracellular matrix (e.g., amyloid P-component, apolipoprotein E, or glycosaminoglycans), and local physical properties, including pH of the tissue. Monomeric proteins appear to go through an oligomeric aggregation step and then form higher order polymers. Once the polymers reach a critical size, they become insoluble and deposit in

TABLE 16-1

AMYLOID FIBRIL PROTEINS AND THEIR CLINICAL SYNDROMES

TERM	PRECURSOR	CLINICAL SYNDROME	CLINICAL INVOLVEMENT
	Systemic Amyloidoses		
AL	Immunoglobulin light chain	Primary or myeloma associated[a]	Any
AH	Immunoglobulin heavy chain	Primary or myeloma associated (rare)	Any
AA	Serum amyloid A protein	Secondary; reactive[b]	Renal, any
$A\beta_2M$	β_2-Microglobulin	Hemodialysis-associated	Synovial membrane, bone
ATTR	Transthyretin	Familial (mutant) Senile systemic (wild type)	Cardiac, peripheral and autonomic nerves
AApoAI	Apolipoprotein AI	Familial	Hepatic, renal
AApoAII	Apolipoprotein AII	Familial	Renal
AGel	Gelsolin	Familial	Corneas, cranial nerves, renal
AFib	Fibrinogen Aα	Familial	Renal
ALys	Lysozyme	Familial	Renal
ALECT2	Leukocyte chemotactic factor 2	?	Renal
	Localized Amyloidoses		
Aβ	Amyloid β protein	Alzheimer's disease; Down syndrome	CNS
ACys	Cystatin C	Cerebral amyloid angiopathy	CNS, vascular
APrP	Prion protein	Spongiform encephalopathies	CNS
AIAPP	Islet amyloid polypeptide (amylin)	Diabetes-associated	Pancreas
ACal	Calcitonin	Medullary carcinoma of the thyroid	Thyroid
AANF	Atrial natriuretic factor	Age-related	Cardiac atria
APro	Prolactin	Endocrinopathy	Pituitary

[a]Localized deposits can occur in skin, conjunctiva, urinary bladder, and tracheobronchial tree.
[b]Secondary to chronic inflammation or infection, or to a hereditary periodic fever syndrome, e.g., familial Mediterranean fever.

extracellular tissue sites as fibrils. These large macromolecular deposits interfere with organ function and, due to cellular uptake of oligomeric amyloid precursors, may be toxic to target cells.

The clinical syndromes of the amyloidoses are associated with relatively nonspecific alterations in routine laboratory tests. Blood counts are usually normal, although the erythrocyte sedimentation rate is frequently elevated. Patients with renal involvement will usually have proteinuria, which can be as much as 30 g/d, producing hypoalbuminemia that can be profound. Patients with cardiac involvement will often have elevation of brain natriuretic peptide (BNP), pro-BNP, and troponin. These can be useful for monitoring disease activity and have been proposed as prognostic factors; they can be falsely elevated in the presence of renal insufficiency. Patients with liver involvement, even when it is advanced, usually develop cholestasis with an elevated alkaline phosphatase but minimal elevation of the transaminases and preservation of synthetic function. In AL amyloidosis, endocrinopathies can occur, with laboratory testing demonstrating hypothyroidism, hypoadrenalism, or even hypopituitarism. None of these findings are specific for amyloidosis. Thus, a diagnosis of amyloidosis rests upon a tissue biopsy that, after Congo red staining, shows "apple-green" birefringence on polarization microscopy.

AL AMYLOIDOSIS

ETIOLOGY AND INCIDENCE

AL amyloidosis is most frequently caused by a clonal expansion of plasma cells in the bone marrow that secrete a monoclonal immunoglobulin LC that deposits as amyloid fibrils in tissues. It may be purely serendipitous whether the clonal plasma cells produce a LC that misfolds and leads to AL amyloidosis, or folds properly, allowing the cells to inexorably expand over time and develop into multiple myeloma. It is also possible that the two processes have diverse molecular etiologies. AL amyloidosis can occur with multiple myeloma or other B lymphoproliferative diseases, including non-Hodgkin's lymphoma and Waldenström's macroglobulinemia. AL amyloidosis is the

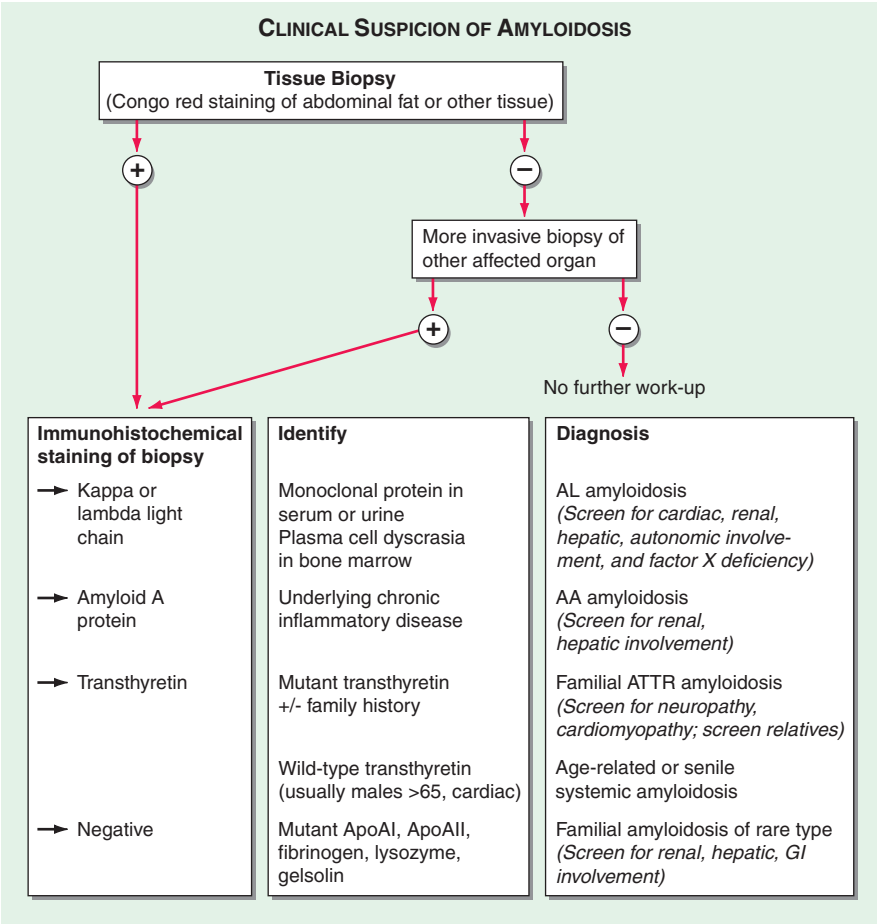


FIGURE 16-1
Algorithm for the diagnosis of amyloidosis and determination of type: Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; GI, gastrointestinal.

most common type of systemic amyloidosis in North America. Its incidence has been estimated at 4.5 per 100,000; however, ascertainment continues to be inadequate, and the true incidence may be much higher. AL amyloidosis, like other plasma cell diseases, usually occurs after age 40 and is often rapidly progressive and fatal if untreated.

PATHOLOGY AND CLINICAL FEATURES OF AL AMYLOIDOSIS

Amyloid deposits are usually widespread in AL amyloidosis and can be present in the interstitium of any organ outside of the central nervous system. The amyloid fibril deposits are composed of intact 23-kDa monoclonal Ig LCs or smaller fragments, 11–18 kDa in size, representing the variable (V) region alone, or the V region and a portion of the constant (C) region. Although all kappa and lambda LC subtypes have been identified in AL amyloid fibrils, lambda subtypes predominate. The lambda 6 subtype appears to have unique structural properties that predispose it to fibril formation, often in the kidney.

AL amyloidosis is usually a rapidly progressive disease that presents with a pleiotropic set of clinical syndromes, recognition of which is key to initiating appropriate workup. Nonspecific symptoms of fatigue and weight loss are common; however, the diagnosis is rarely considered until symptoms referable to a specific organ develop. The kidneys are the most frequently affected organ, in 70–80% of patients. Renal amyloidosis is usually manifested as proteinuria, often in the nephrotic range and associated with significant hypoalbuminemia, secondary hypercholesterolemia, and edema or anasarca. In some patients, tubular rather than glomerular deposition of amyloid can produce azotemia without significant proteinuria. The heart is the second most commonly affected organ, in 50–60% of patients, and the leading cause of mortality. Early on, the electrocardiogram may show low voltage in the limb leads, with a pseudo-infarct pattern. Eventually, the echocardiogram will display concentrically thickened ventricles and diastolic dysfunction, leading to a restrictive cardiomyopathy; systolic function is preserved until late in the disease. A "sparkly" appearance is usually not seen using modern high-resolution echocardiography equipment. Cardiac MRI can show an increased wall thickness and also a



FIGURE 16-2
Clinical signs of AL amyloidosis. ***A.*** Macroglossia. ***B.*** Periorbital ecchymoses. ***C.*** Fingernail dystrophy.

characteristic subendocardial enhancement with gadolinium. Nervous system symptoms include a peripheral sensory neuropathy and/or autonomic dysfunction with gastrointestinal motility disturbances (early satiety, diarrhea, constipation) and orthostatic hypotension. Macroglossia, with an enlarged, indented, or immobile tongue, is pathognomonic of AL amyloidosis but is seen only in ~10% of patients. Liver involvement causes cholestasis and hepatomegaly. The spleen is frequently involved, and there may be functional hyposplenism in the absence of significant splenomegaly. Many patients have "easy bruising" due to amyloid deposits in capillaries or to deficiency of clotting factor X, which can bind to amyloid fibrils; cutaneous ecchymoses appear, particularly around the eyes, giving the "raccoon-eye" sign. Other findings include nail dystrophy, alopecia, and amyloid arthropathy with thickening of synovial membranes in wrists and shoulders **(Fig. 16-2)**. The presence of a multisystem illness or general fatigue along with any of these clinical syndromes should prompt a workup for amyloidosis.

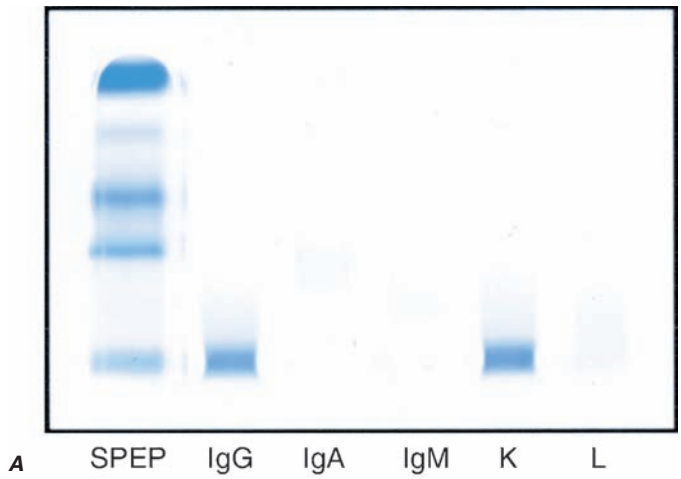
DIAGNOSIS

Identification of the underlying B lymphoproliferative process and clonal LC is key to the diagnosis of AL amyloidosis. The serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) are NOT useful screening tests if AL amyloidosis is suspected because the clonal LC or whole immunoglobulin, unlike in multiple myeloma, is often not present in sufficient quantity in the serum to produce a monoclonal "M-spike" or in the urine to cause LC (Bence Jones) proteinuria. However, more than 90% of patients have a serum or urine monoclonal LC or whole immunoglobulin that can be detected by immunofixation electrophoresis of serum (SIFE) or urine (UIFE) **(Fig. 16-3*A*)**. Assaying for free immunoglobulin LCs circulating in the serum unbound to heavy chains using commercially available nephelometric (FreeLite©) assay demonstrates an elevation and abnormal free kappa: lambda ratio in more than 75% of patients. Examining the ratio as well as the absolute amount is essential, because in renal insufficiency LC clearance is reduced, and both types of LCs will be elevated. In addition, an increased percentage of plasma cells in the bone marrow, typically 5–5% of nucleated cells, is noted in about 90% of patients. Kappa or lambda clonality can be demonstrated by flow cytometry, immunohistochemical staining, or by in situ hybridization for LC mRNA (Fig. 16-3*B*).

A monoclonal serum protein by itself is not diagnostic of amyloidosis, since monoclonal gammopathy of uncertain significance (MGUS) is common in older patients. However, when MGUS is present in patients with biopsy-proven amyloidosis, the AL type should be strongly suspected. Similarly, patients thought to have "smoldering myeloma" because of modest elevation of bone marrow plasma cells should be screened for AL amyloidosis if they have evidence of organ dysfunction. Accurate typing is essential for appropriate treatment. Immunohistochemical staining of the amyloid deposits is useful if they bind one light chain antibody in preference to the other; some AL deposits bind many antisera nonspecifically. Immunoelectron microscopy is more reliable and mass-spectrometry-based microsequencing of small amounts of protein extracted from fibril deposits can also be done. In ambiguous cases, other forms of amyloidosis should be thoroughly excluded with appropriate genetic and other testing.

TREATMENT **AL Amyloidosis**

Extensive multisystem involvement typifies AL amyloidosis, and median survival with no treatment is usually only about 1–2 years from the time of diagnosis. Current therapies target the clonal bone marrow plasma cells using approaches employed for multiple myeloma.



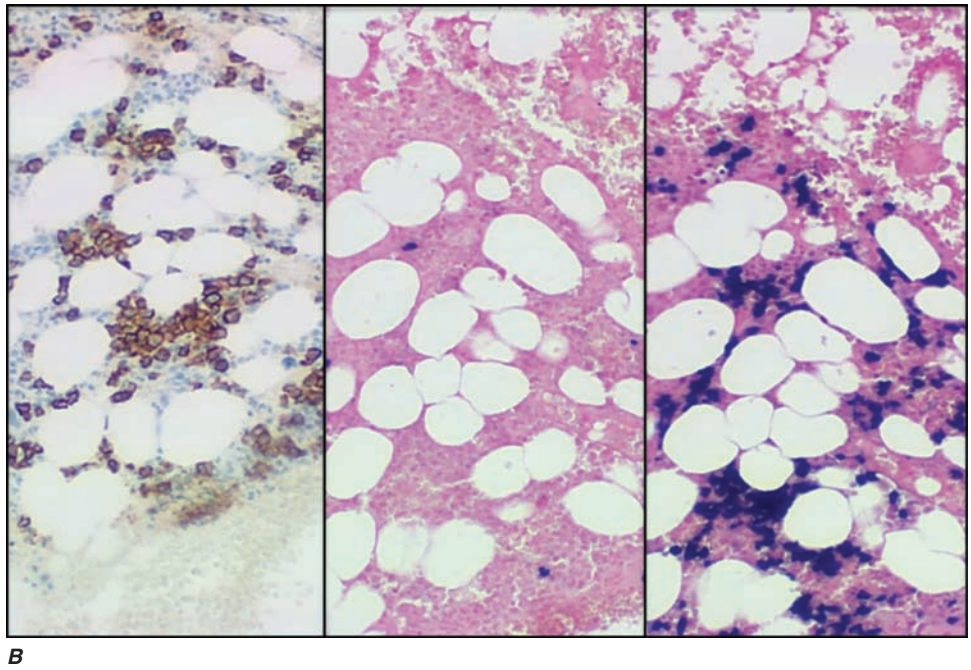


FIGURE 16-3

Laboratory features of AL amyloidosis. ***A.*** Serum immunofixation electrophoresis reveals an IgGκ monoclonal protein in this example; the serum protein electrophoresis is often normal. ***B.*** Bone marrow biopsy sections from another patient, stained with antibody to CD138 (syndecan, highly expressed on plasma cells) by immunohistochemistry (left panel). The middle and right panels are stained using in situ hybridization with fluorescein-tagged probes (Ventana Medical Systems) binding to κ and λ mRNA respectively in plasma cells. (*Photomicrograph courtesy of C. O'Hara; with permission.*)

Treatment with cyclic oral melphalan and prednisone can decrease the plasma cell burden, but produces complete hematologic remission in only a few percent of patients and minimal organ responses and improvement in survival (median 2 years), and it is no longer widely used. The substitution of dexamethasone for prednisone produces a higher response rate and more durable remissions, although dexamethasone is not always well tolerated by patients with significant edema or cardiac disease. High-dose intravenous melphalan followed by autologous stem cell transplantation (HDM/SCT) produces complete hematologic responses in about 40% of treated patients, as measured by complete loss (CR) of clonal plasma cells in the bone marrow and disappearance of the monoclonal LC by IFE and assay for free LCs. Hematologic responses can be followed in the subsequent 6–12 months by improvement in organ function and quality of life. The CRs after HDM/SCT appear to be more durable than those seen in multiple myeloma, with remissions continuing in some patients

beyond 15 years without additional treatment. Unfortunately, only about half of AL amyloidosis patients are eligible for such aggressive treatment, and even at specialized treatment centers, peritransplant mortality is higher than for other hematologic diseases because of impaired organ function. Amyloid cardiomyopathy, poor nutritional status, impaired performance status, and multiple-organ disease contribute to excess morbidity and mortality. The bleeding diathesis due to adsorption of clotting factor X to amyloid fibrils also confers high mortality during myelosuppressive therapy; however, this syndrome occurs in only a few percent of patients. The single randomized multicenter trial comparing oral melphalan and dexamethasone to HDM/SCT to date failed to show a benefit to dose-intensive treatment, although the transplant-related mortality in this study was very high.

For patients with impaired cardiac function or arrhythmias due to amyloid involvement of the myocardium, median survival is only about 6 months without treatment, and stem cell mobilization and high-dose chemotherapy are dangerous. In these patients, cardiac transplantation can be performed, followed by treatment with HDM/SCT to prevent amyloid deposition in the transplanted heart or other organs.

Recently, novel agents have been investigated for treatment of plasma cell diseases. The immunomodulators thalidomide and lenalidomide have activity; lenalidomide is well tolerated in doses lower than those used for myeloma and, in combination with dexamethasone, produces complete hematologic remissions and improvement in organ function. The proteasome inhibitor bortezomib has also been found to be effective in single- and multicenter trials. Combination therapy trials are now under development, and studies are examining the as yet unproven role of induction and maintenance treatment. Clinical trials are essential for improving therapy for this rare disease.

Supportive care is important for patients with any type of amyloidosis. For nephrotic syndrome, diuretics and supportive stockings can ameliorate edema; angiotensin-converting enzyme inhibitors should be used with caution and have not been shown to slow renal disease progression. Congestive heart failure due to amyloid cardiomyopathy is also best treated with diuretics; it is important to note that digitalis, calcium channel blockers, and beta blockers are relatively contraindicated as they can interact with amyloid fibrils and produce heart block and worsening heart failure. Amiodarone has been used for atrial and ventricular arrhythmias. Automatic implantable defibrillators have reduced effectiveness due to the thickened myocardium, but they can benefit some patients. Atrial ablation is an effective approach for atrial fibrillation. For conduction abnormalities, ventricular pacing may be indicated. Atrial contractile dysfunction is common in amyloid cardiomyopathy and is an indication for anticoagulation even in the absence of atrial fibrillation. Autonomic neuropathy can be treated with α agonists such as midodrine to support the blood pressure; gastrointestinal dysfunction may respond to motility or bulk agents. Nutritional supplementation, either orally or parenterally, is also important.

In localized AL, amyloid deposits can be produced by clonal plasma cells infiltrating local sites in the airways, bladder, skin, or lymph nodes (Table 16-1). Deposits may respond to surgical intervention or radiation therapy; systemic treatment is generally not appropriate. Patients should be referred to a center familiar with management of these rare manifestations of amyloidosis.

AA AMYLOIDOSIS

ETIOLOGY AND INCIDENCE

AA amyloidosis can occur in association with almost any chronic inflammatory state (e.g., rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever [Chap. 15] or other periodic fever syndromes) or chronic infections such as tuberculosis or subacute bacterial endocarditis. In the United States and Europe, AA amyloidosis has become less common, occurring in <2% of patients with these diseases, presumably because of advances in anti-inflammatory and antimicrobial therapies. It has also been described in association with Castleman's disease, and patients with AA amyloidosis should have CT scanning to look for such tumors, as well as serologic and microbiologic studies. AA amyloidosis can also be seen without any identifiable underlying disease. AA is the only type of systemic amyloidosis that occurs in children.

PATHOLOGY AND CLINICAL FEATURES

Deposits are more limited in AA amyloidosis than in AL amyloidosis; they usually begin in the kidneys. Hepatomegaly, splenomegaly, and autonomic neuropathy can also occur as the disease progresses; cardiomyopathy occurs albeit rarely. However, the symptoms and signs cannot be reliably distinguished from those of AL amyloidosis. AA amyloid fibrils are usually composed of an 8-kDa, 76-amino-acid *N*-terminal portion of a 12-kDa precursor protein, serum amyloid A (SAA). SAA is an acute-phase apoprotein synthesized in the liver and transported by high-density lipoprotein, HDL3, in the plasma. Several years of an underlying inflammatory disease causing chronic elevation of SAA usually precedes fibril formation, although infections can lead to AA deposition more rapidly.

TREATMENT **AA Amyloidosis**

The primary therapy in AA amyloidosis is treatment of the underlying inflammatory or infectious disease. Treatment that suppresses or eliminates the inflammation or infection also decreases the SAA protein concentration. For familial Mediterranean fever, colchicine in a dose of 1.2–1.8 mg/d is the appropriate treatment. Colchicine has not been helpful for AA amyloidosis of other causes or for other amyloidoses. TNF and IL-1 antagonists can also be effective in syndromes related to cytokine elevation. For this disease, there is also a fibril-specific agent. Eprodisate was designed to interfere with the interaction of AA amyloid protein with glycosaminoglycans in tissues and prevent or disrupt fibril formation. This drug is well tolerated and delays progression of AA renal disease, regardless of the underlying inflammatory process. Eprodisate is awaiting FDA approval.

AF AMYLOIDOSIS

The familial amyloidoses are autosomal dominant diseases in which a variant plasma protein forms amyloid deposits, beginning in midlife. These diseases are rare, with an estimated incidence of <1 per 100,000 in the United States, although there are isolated areas of Portugal, Sweden, and Japan where founder effects have led to a much higher incidence of the disease. The most common form of AF is caused by mutation of the abundant plasma protein transthyretin (TTR, also known as *prealbumin*). More than 100 TTR mutations are known, and most are associated with ATTR amyloidosis. One variant, V122I, has a carrier frequency that may be as high as 4% in the African-American population and is associated with late-onset cardiac amyloidosis. The actual incidence and penetrance of disease in the African-American population is the subject of ongoing research, but it would be wise to consider this in the differential diagnosis of African-American patients who present with concentric cardiac hypertrophy and evidence of diastolic dysfunction, particularly in the absence of a history of hypertension. Even wild-type TTR can form fibrils, leading to so-called senile systemic amyloidosis (SSA) in older patients. It can be found in up to 25% of autopsies in patients older than age 80 years, and it can produce a clinical syndrome of amyloid cardiomyopathy that is similar to that occurring in younger patients carrying a mutant TTR. Other familial amyloidoses, caused by variant apolipoproteins AI or AII, gelsolin, fibrinogen Aα, or lysozyme, are reported in only a few families worldwide. New amyloidogenic serum proteins continue to be identified periodically, including recently the leukocyte chemotactic factor LECT2.

In ATTR and in other forms of familial amyloidosis, the variant structure of the precursor protein is the key factor in fibril formation. The role of aging is intriguing, since patients born with the variant proteins do not have clinically apparent disease until middle age, despite the lifelong presence of the abnormal protein. Further evidence of an age-related "trigger" is the occurrence of SSA in the elderly, caused by the deposition of fibrils derived from normal TTR.

CLINICAL FEATURES AND DIAGNOSIS

AF amyloidosis has a variable presentation but is usually consistent within affected kindreds with the same mutant protein. A family history makes AF more likely, but many patients present sporadically with new mutations. ATTR usually presents as a syndrome of familial amyloidotic polyneuropathy or familial amyloidotic cardiomyopathy. Peripheral neuropathy usually begins as a lower-extremity sensory and motor neuropathy and progresses to the upper extremities. Autonomic neuropathy is manifest by gastrointestinal symptoms of diarrhea with weight loss and orthostatic hypotension. Patients with TTR V30M, the most common mutation, have normal echocardiograms but may have conduction defects and require a pacemaker. Patients with TTR T60A and several other mutations have myocardial thickening similar to that caused by AL amyloidosis, although heart failure is less common and the prognosis is better. Vitreous opacities caused by amyloid deposits are pathognomonic of ATTR amyloidosis.

Typical syndromes associated with other forms of AF included renal amyloidosis with mutant fibrinogen, lysozyme, or apolipoproteins, or hepatic amyloidosis with apolipoprotein AI, and amyloidosis of cranial nerves and cornea with gelsolin.

Patients with AF amyloidosis can present with clinical syndromes that mimic those of patients with AL, and AF carriers can develop AL, or conversely, AF patients can develop a MGUS. Thus, it is important to screen for both plasma cell disorders and for mutations in some patients with amyloidosis. Variant TTR proteins can usually be detected by isoelectric focusing, but DNA sequencing is now standard for diagnosis of ATTR and the other AF mutations.

TREATMENT **ATTR Amyloidosis**

Without intervention, survival after ATTR disease onset is 5–15 years. Orthotopic liver transplantation removes the major source of variant TTR production and replaces it with a source of normal TTR; it also arrests disease progression and leads to improvement in autonomic and peripheral neuropathy in some patients. Cardiomyopathy often

does not improve, and in some patients it can worsen after liver transplantation, perhaps due to deposition of wild-type TTR as seen in SSA. Compounds have been identified that stabilize TTR in a nonpathogenic tetrameric conformation in vitro and are undergoing clinical testing in multicenter trials.

$A\beta_2M$ AMYLOIDOSIS

$A\beta_2M$ amyloidosis is composed of β_2-microglobulin, the invariant chain of class I human leukocyte antigens, and produces rheumatologic manifestations in patients on long-term hemodialysis. β_2-Microglobulin is excreted by the kidney, and levels become elevated in ESRD. The molecular mass of β_2M is 11.8 kDa, above the cutoff of some dialysis membranes. The incidence of this disease appears to be declining with newer high-flow dialysis techniques.

$A\beta_2M$ amyloidosis usually presents with carpal tunnel syndrome, persistent joint effusions, spondyloarthropathy, or cystic bone lesions. Carpal tunnel syndrome is often the first symptom of disease. In the past, persistent joint effusions accompanied by mild discomfort were seen in up to 50% of patients on dialysis for more than 12 years. Involvement is bilateral, and large joints (shoulders, knees, wrists, and hips) are more frequently affected. The synovial fluid is noninflammatory, and β_2M amyloid can be found if the sediment is stained with Congo red. Although less common, visceral β_2M amyloid deposits do occasionally occur in the gastrointestinal tract, heart, tendons, and subcutaneous tissues of the buttocks. There is no specific therapy for $A\beta_2M$ amyloidosis, but cessation of dialysis after renal allografting may lead to symptomatic improvement.

SUMMARY

A diagnosis of amyloidosis should be considered in patients with unexplained nephropathy, cardiomyopathy (particularly with diastolic dysfunction), neuropathy (either peripheral or autonomic), enteropathy, or the pathognomonic soft tissue findings of macroglossia or periorbital ecchymoses. Pathologic identification of amyloid fibrils can be made using Congo red staining of aspirated abdominal fat or of an involved organ biopsy specimen. Accurate typing using a combination of immunologic, biochemical, and genetic testing is essential to choosing the appropriate therapy (see algorithm for workup, Fig. 16-1). Tertiary referral centers can provide specialized diagnostic techniques and access to clinical trials for patients with these rare diseases.

CHAPTER 17

POLYMYOSITIS, DERMATOMYOSITIS, AND INCLUSION BODY MYOSITIS

Marinos C. Dalakas

The inflammatory myopathies represent the largest group of acquired and potentially treatable causes of skeletal muscle weakness. They are classified into three major groups: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

CLINICAL FEATURES

The prevalence of the inflammatory myopathies is estimated at 1 in 100,000. PM as a stand-alone entity is a rare disease. DM affects both children and adults and women more often than men. IBM is three times more frequent in men than in women, more common in whites than blacks, and is most likely to affect persons aged >50 years.

These disorders present as progressive and symmetric muscle weakness except for IBM, which can have an asymmetric pattern. Patients usually report increasing difficulty with everyday tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, stepping onto a curb, lifting objects, or combing hair. Fine-motor movements that depend on the strength of distal muscles, such as buttoning a shirt, sewing, knitting, or writing, are affected only late in the course of PM and DM, but fairly early in IBM. Falling is common in IBM because of early involvement of the quadriceps muscle, with buckling of the knees. Ocular muscles are spared, even in advanced, untreated cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be questioned. Facial muscles are unaffected in PM and DM, but mild facial muscle weakness is common in patientswith IBM. In all forms of inflammatory myopathy, pharyngeal and neck-flexor muscles are often involved, causing dysphagia or difficulty in holding up the head (*head drop*). In advanced and rarely in acute cases, respiratory muscles may also be affected. Severe weakness, if untreated, is almost always associated with muscle wasting. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles, especially in IBM, where atrophy of the quadriceps and the distal muscles is common. Myalgia and muscle tenderness may occur in a small number of patients, usually early in the disease, and particularly in DM associated with connective tissue disorders. Weakness in PM and DM progresses subacutely over a period of weeks or months and rarely acutely; by contrast, IBM progresses very slowly, over years, simulating a late-life muscular dystrophy or slowly progressive motor neuron disorder.

SPECIFIC FEATURES

(Table 17-1)

Polymyositis

The actual onset of PM is often not easily determined, and patients typically delay seeking medical advice for several weeks or even months. This is in contrast to DM, in which the rash facilitates early recognition (see next). PM mimics many other myopathies and is a diagnosis of exclusion. It is a subacute inflammatory myopathy affecting adults, and rarely children, who *do not have* any of the following: rash, involvement of the extraocular and facial muscles, family history of a neuromuscular disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, muscular dystrophy, biochemical muscle disorder (deficiency of a muscle enzyme), or IBM as excluded by muscle biopsy analysis (see next). As an isolated entity, PM is a rare (and overdiagnosed) disorder; more commonly, PM occurs in association with a systemic autoimmune or connective tissue disease, or with a known viral or bacterial infection. Drugs, especially

TABLE 17-1

FEATURES ASSOCIATED WITH INFLAMMATORY MYOPATHIES

CHARACTERISTIC	POLYMYOSITIS	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
Age at onset	>18 years	Adulthood and childhood	>50 years
Familial association	No	No	Yes, in some cases
Extramuscular manifestations	Yes	Yes	Yes
Associated conditions			
Connective tissue diseases	Yes[a]	Scleroderma and mixed connective tissue disease (overlap syndromes)	Yes, in up to 20% of cases[a]
Systemic autoimmune diseases[b]	Frequent	Infrequent	Infrequent
Malignancy	No	Yes, in up to 15% of cases	No
Viruses	Yes[c]	Unproven	Yes[c]
Drugs[d]	Yes	Yes, rarely	No
Parasites and bacteria[e]	Yes	No	No

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-I (human T cell lymphotropic virus type I).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

D-penicillamine, statins, or zidovudine (AZT), may also trigger an inflammatory myopathy similar to PM.

Dermatomyositis

DM is a distinctive entity identified by a characteristic rash accompanying, or more often preceding, muscle weakness. The rash may consist of a blue-purple discoloration on the upper eyelids with edema (heliotrope rash), a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (*Gottron's sign*). The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a *V sign*), or back and shoulders (*shawl sign*), and may worsen after sun exposure. In some patients, the rash is pruritic, especially on the scalp, chest, and back. Dilated capillary loops at the base of the fingernails are also characteristic. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling *mechanic's hands*. The weakness can be mild, moderate, or severe enough to lead to quadriparesis. At times, the muscle strength appears normal, hence the term *dermatomyositis sine myositis*. When muscle biopsy is performed in such cases, however, significant perivascular and perimysial inflammation is often seen.

DM usually occurs alone but may overlap with scleroderma and mixed connective tissue disease. Fasciitis and thickening of the skin, similar to that seen in chronic cases of DM, have occurred in patients with the *eosinophilia-myalgia syndrome* associated with the ingestion of contaminated L-tryptophan.

Inclusion body myositis

In patients ≥50 years of age, IBM is the most common of the inflammatory myopathies. It is often misdiagnosed as PM and is suspected only later when a patient with presumed PM does not respond to therapy. Weakness and atrophy of the distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue to early diagnosis. Some patients present with falls because their knees collapse due to early quadriceps weakness. Others present with weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold objects such as golf clubs or perform tasks such as turning keys or tying knots. On occasion, the weakness and accompanying atrophy can be asymmetric and selectively involve the quadriceps, iliopsoas, triceps, biceps, and finger flexors, resembling a lower motor neuron disease. Dysphagia is common, occurring in up to 60% of IBM patients, and may lead to episodes of choking. Sensory examination is generally normal; some patients have mildly diminished vibratory sensation at the ankles

that presumably is age-related. The pattern of distal weakness, which superficially resembles motor neuron or peripheral nerve disease, results from the myopathic process affecting distal muscles selectively. Disease progression is slow but steady, and most patients require an assistive device such as cane, walker, or wheelchair within several years of onset.

In at least 20% of cases, IBM is associated with systemic autoimmune or connective tissue diseases. Familial aggregation of typical IBM may occur; such cases have been designated as *familial inflammatory IBM*. This disorder is distinct from *hereditary inclusion body myopathy* (h-IBM), which describes a heterogeneous group of recessive, and less frequently dominant, inherited syndromes; the h-IBMs are noninflammatory myopathies. A subset of h-IBM that spares the quadriceps muscles has emerged as a distinct entity. This disorder, originally described in Iranian Jews and now seen in many ethnic groups, is linked to chromosome 9p1 and results from mutations in the UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (*GNE*) gene.

ASSOCIATED CLINICAL FINDINGS

Extramuscular manifestations

These may be present to a varying degree in patients with PM or DM, and include:

1. *Systemic symptoms*, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon, especially when inflammatory myopathy is associated with a connective tissue disorder.
2. *Joint contractures*, mostly in DM and especially in children.
3. *Dysphagia and gastrointestinal symptoms*, due to involvement of oropharyngeal striated muscles and upper esophagus, especially in DM and IBM.
4. *Cardiac disturbances*, including atrioventricular conduction defects, tachyarrhythmias, dilated cardiomyopathy, a low ejection fraction, and congestive heart failure, may rarely occur, either from the disease itself or from hypertension associated with long-term use of glucocorticoids.
5. *Pulmonary dysfunction*, due to weakness of the thoracic muscles, interstitial lung disease, or drug-induced pneumonitis (e.g., from methotrexate), which may cause dyspnea, nonproductive cough, and aspiration pneumonia. Interstitial lung disease may precede myopathy or occur early in the disease and develops in up to 10% of patients with PM or DM, most of whom have antibodies to t-RNA synthetases, as described next.
6. *Subcutaneous calcifications*, in DM, sometimes extruding on the skin and causing ulcerations andinfections.
7. *Arthralgias*, synovitis, or deforming arthropathy with subluxation in the interphalangeal joints can occur in some patients with DM and PM who have Jo-1 antibodies (see next).

Association with malignancies

Although all the inflammatory myopathies can have a chance association with malignant lesions, especially in older age groups, the incidence of malignant conditions appears to be specifically increased only in patients with DM and not in those with PM or IBM. The most common tumors associated with DM are ovarian cancer, breast cancer, melanoma, colon cancer, and non-Hodgkin lymphoma. The extent of the search that should be conducted for an occult neoplasm in adults with DM depends on the clinical circumstances. Tumors in these patients are usually uncovered by abnormal findings in the medical history and physical examination and not through an extensive blind search. The weight of evidence argues against performing expensive, invasive, and nondirected tumor searches. A complete annual physical examination with pelvic, breast (mammogram, if indicated), and rectal examinations (with colonoscopy according to age and family history); urinalysis; complete blood count; blood chemistry tests; and a chest film should suffice in most cases. In Asians, nasopharyngeal cancer is common, and a careful examination of ears, nose, and throat is indicated. If malignancy is clinically suspected, screening with whole-body PET scan should be considered.

Overlap syndromes

These describe the association of inflammatory myopathies with connective tissue diseases. A well-characterized overlap syndrome occurs in patients with DM who also have manifestations of systemic sclerosis or mixed connective tissue disease, such as sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits (Table 17-1). By contrast, signs of rheumatoid arthritis, systemic lupus erythematosus, or Sjögren's syndrome are very rare in patients with DM. Patients with the overlap syndrome of DM and systemic sclerosis may have a specific antinuclear antibody, the anti-PM/Scl, directed against a nucleolar-protein complex.

PATHOGENESIS

An autoimmune etiology of the inflammatory myopathies is indirectly supported by an association with other autoimmune or connective tissue diseases; the presence of various autoantibodies; an association with specific major histocompatibility complex (MHC) genes; demonstration of T cell–mediated myocytotoxicity or complement-mediated microangiopathy; and a response to immunotherapy.

Autoantibodies and immunogenetics

Various autoantibodies against nuclear antigens (antinuclear antibodies) and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathies. The antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti-signal-recognition particles). The antibody directed against the histidyl-transfer RNA synthetase, called *anti-Jo-1*, accounts for 75% of all the antisynthetases and is clinically useful because up to 80% of patients with anti-Jo-1 antibodies have interstitial lung disease. Some patients with the anti-Jo-1 antibody also have Raynaud's phenomenon, nonerosive arthritis, and the MHC molecules DR3 and DRw52. DR3 haplotypes (molecular designation DRB1*0301, DQB1*0201) occur in up to 75% of patients with PM and IBM, whereas in juvenile DM there is an increased frequency of DQA1*0501 (Chap. 2).

Immunopathologic mechanisms

In DM, humoral immune mechanisms are implicated, resulting in a microangiopathy and muscle ischemia **(Fig. 17-1)**. Endomysial inflammatory infiltrates are composed of B cells located in proximity to CD4 T cells, plasmacytoid dendritic cells, and macrophages; there is a relative absence of lymphocytic invasion of nonnecrotic muscle fibers. Activation of the complement C5b-9 membranolytic attack complex is thought to be a critical early event that triggers release of proinflammatory cytokines and chemokines, induces expression of vascular cell adhesion molecule (VCAM) 1 and intercellular adhesion molecule (ICAM) 1 on endothelial cells, and facilitates migration of activated lymphoid cells to

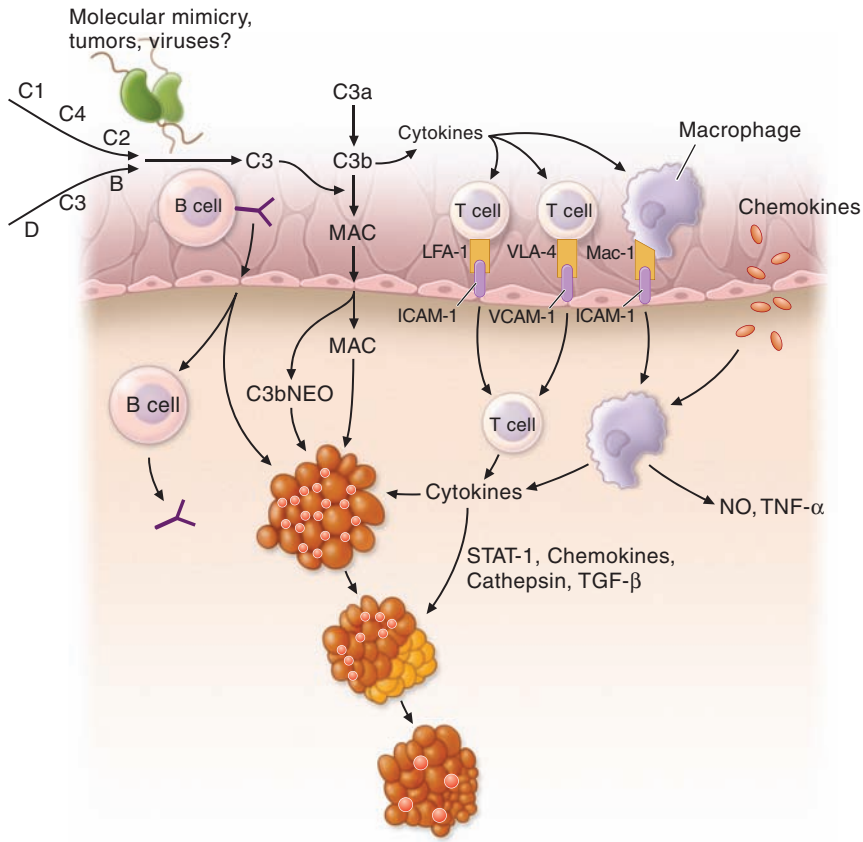


FIGURE 17-1

Immunopathogenesis of dermatomyositis. Activation of complement, possibly by autoantibodies (Y), against endothelial cells and formation of C3 via the classic or alternative pathway. Activated C3 leads to formation of C3b, C3bNEO, and membrane attack complexes (MAC), which are deposited in and around the endothelial cell wall of the endomysial capillaries. Deposition of MAC leads to destruction of capillaries, ischemia, or microinfarcts, most prominent in the periphery of the fascicles, and perifascicular atrophy. B cells, plasmacytoid dendritic cells, CD4 T cells, and macrophages traffic from the circulation to the muscle. Endothelial expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) is induced by cytokines released by the mononuclear cells. Integrins, specifically very late activation antigen (VLA)-4 and lymphocyte function–associated antigen (LFA)-1, bind VCAM and ICAM and promote T cell and macrophage infiltration of muscle through the endothelial cell wall.

the perimysial and endomysial spaces. Necrosis of the endothelial cells, reduced numbers of endomysial capillaries, ischemia, and muscle-fiber destruction resembling microinfarcts occur. The remaining capillaries often have dilated lumens in response to the ischemic process. Larger intramuscular blood vessels may also be affected in the same pattern. Residual perifascicular atrophy reflects the endofascicular hypoperfusion that is prominent in the periphery of muscle fascicles. Increased expression of type I interferon-inducible proteins is also noted in these regions.

By contrast, in PM and IBM a mechanism of T cell–mediated cytotoxicity is likely. CD8 T cells, along with macrophages, initially surround and eventually invade and destroy healthy, nonnecrotic muscle fibers that aberrantly express class I MHC molecules. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells and macrophages. The CD8/MHC-I complex is characteristic of PM and IBM; its detection can aid in confirming the histologic diagnosis of PM, as discussed next. The cytotoxic CD8 T cells contain perforin and granzyme granules directed toward the surface of the muscle fibers and capable of inducing myonecrosis. Analysis of T cell receptor molecules expressed by the infiltrating CD8 cells has revealed clonal expansion and conserved sequences in the antigen-binding region, both suggesting an antigen-driven T cell response. Whether the putative antigens are endogenous (e.g., muscle) or exogenous (e.g., viral) sequences is unknown. Viruses have not been identified within the muscle fibers. Co-stimulatory molecules and their counterreceptors, which are fundamental for T cell activation and antigen recognition, are strongly upregulated in PM and IBM. Key molecules involved in T cell–mediated cytotoxicity are depicted in **Fig. 17-2**.

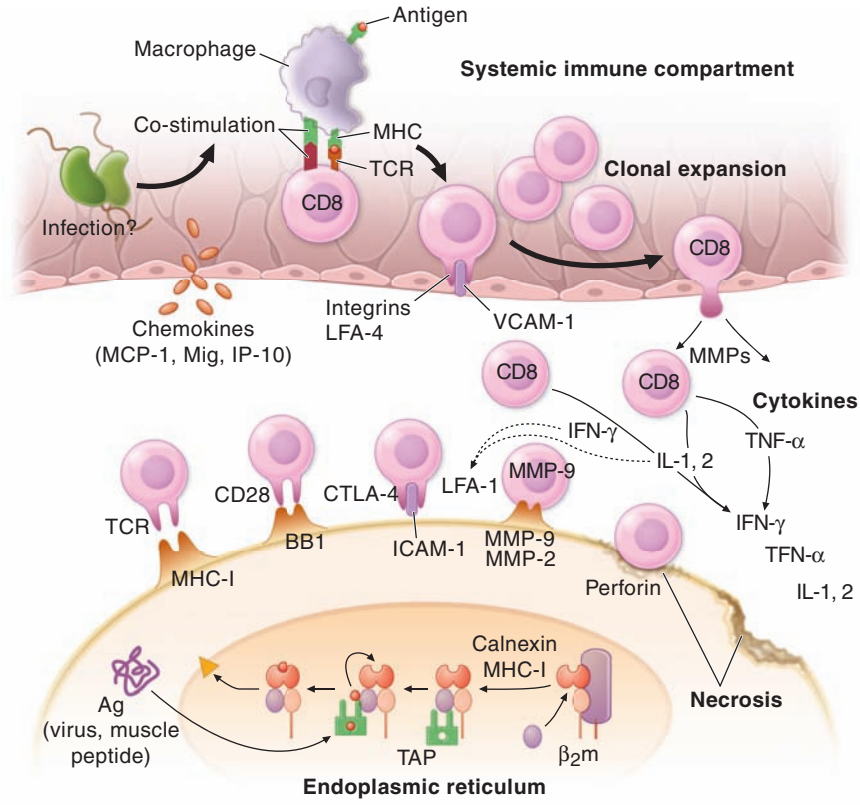


FIGURE 17-2

Cell-mediated mechanisms of muscle damage in polymyositis (PM) and inclusion body myositis (IBM). Antigen-specific CD8 cells are expanded in the periphery, cross the endothelial barrier, and bind directly to muscle fibers via T cell receptor (TCR) molecules that recognize aberrantly expressed MHC-I. Engagement of co-stimulatory molecules (BB1 and ICOSL) with their ligands (CD28, CTLA-4, and ICOS), along with ICAM-1/LFA-1, stabilize the CD8–muscle fiber interaction. Metalloproteinases (MMPs) facilitate the migration of T cells and their attachment to the muscle surface. Muscle fiber necrosis occurs via perforin granules released by the autoaggressive T cells. A direct myocytotoxic effect exerted by the cytokines interferon (IFN) γ, interleukin (IL) 1, or tumor necrosis factor (TNF) α may also play a role. Death of the muscle fiber is mediated by necrosis. MHC class I molecules consist of a heavy chain and a light chain (β_2 microglobulin [β_2m]) complexed with an antigenic peptide that is transported into the endoplasmic reticulum by TAP proteins (Chap. 2).

The role of nonimmune factors in IBM

In IBM, the presence of Congo red–positive amyloid deposits within some vacuolated muscle fibers and abnormal mitochondria with cytochrome oxidase–negative fibers suggest that, in addition to the autoimmune component, there is also a degenerative process. Similar to Alzheimer's disease, the intracellular amyloid deposits in IBM are immunoreactive against amyloid precursor protein (APP), β-amyloid, chymotrypsin, apolipoprotein E, presenilin, ubiquitin, and phosphorylated tau, but it is unclear whether these deposits, which are also seen in other vacuolar myopathies, are directly pathogenic or represent secondary phenomena. The same is true for the mitochondrial abnormalities, which may also be secondary to the effects of aging or a bystander effect of upregulated cytokines. Expression of cytokines and upregulation of MHC class I by the muscle fibers may cause an endoplasmic reticulum stress response resulting in intracellular accumulation of stressor molecules or misfolded glycoproteins and activation of nuclear factor κB (NF-κB), leading to further cytokine activation.

Association with viral infections and the role of retroviruses

Several viruses, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus, and Epstein-Barr virus, have been indirectly associated with myositis. For the coxsackieviruses, an autoimmune myositis triggered by molecular mimicry has been proposed because of structural homology between histidyl-transfer RNA synthetase that is the target of the Jo-1 antibody (see earlier) and genomic RNA of an animal picornavirus, the encephalomyocarditis virus. Sensitive polymerase chain reaction (PCR) studies, however, have repeatedly failed to confirm the presence of such viruses in muscle biopsies.

The best evidence of a viral connection in PM and IBM is with the retroviruses. Some individuals infected with HIV or with human T cell lymphotropic virus I (HTLV-I) develop PM or IBM; a similar disorder has been described in nonhuman primates infected with the simian immunodeficiency virus. The inflammatory myopathy may occur as the initial manifestation of a retroviral infection, or myositis may develop later in the disease course. Retroviral antigens have been detected only in occasional endomysial macrophages and not within the muscle fibers themselves, suggesting that persistent infection and viral replication within the muscle do not occur. Histologic findings are identical to retroviral-negative PM or IBM. The infiltrating T cells in the muscle are clonally driven and a number of them are retroviral-specific. This disorder should be distinguished from a toxic myopathy related to long-term therapy with AZT, characterized by fatigue, myalgia, mild muscle weakness, and mild elevation of creatine kinase (CK). AZT-induced myopathy, which generally improves when the drug is discontinued, is a mitochondrial disorder characterized histologically by "ragged-red" fibers. AZT inhibits γ-DNA polymerase, an enzyme found solely in the mitochondrial matrix.

DIFFERENTIAL DIAGNOSIS

The clinical picture of the typical skin rash and proximal or diffuse muscle weakness has few causes other than DM. However, proximal muscle weakness without skin involvement can be due to many conditions other than PM or IBM.

Subacute or chronic progressive muscle weakness

This may be due to denervating conditions such as the spinal muscular atrophies or amyotrophic lateral sclerosis. In addition to the muscle weakness, upper motor neuron signs in the latter and signs of denervation detected by electromyography (EMG) aid in the diagnosis. The muscular dystrophies may be additional considerations; however, these disorders usually develop over years rather than weeks or months and rarely present after the age of 30 years. It may be difficult, even with a muscle biopsy, to distinguish chronic PM from a rapidly advancing muscular dystrophy. This is particularly true of facioscapulohumeral muscular dystrophy, dysferlin myopathy, and the dystrophinopathies where inflammatory cell infiltration is often found early in the disease. Such doubtful cases should always be given an adequate trial of glucocorticoid therapy and undergo genetic testing to exclude muscular dystrophy. Identification of the MHC/CD8 lesion by muscle biopsy is helpful to identify cases of PM. Some metabolic myopathies, including glycogen storage disease due to myophosphorylase or acid maltase deficiency, lipid storage myopathies due to carnitine deficiency, and mitochondrial diseases produce weakness that is often associated with other characteristic clinical signs; diagnosis rests upon histochemical and biochemical studies of the muscle biopsy. The endocrine myopathies such as those due to hypercorticosteroidism, hyper- and hypothyroidism, and hyper- and hypoparathyroidism require the appropriate laboratory investigations for diagnosis. Muscle wasting in patients with an underlying neoplasm may be due to disuse, cachexia, or rarely to a paraneoplastic neuromyopathy.

Diseases of the neuromuscular junction, including myasthenia gravis or the Lambert-Eaton myasthenic syndrome, cause fatiguing weakness that also affects ocular and other cranial muscles. Repetitive nerve stimulation and single-fiber EMG studies aid in diagnosis.

Acute muscle weakness

This may be caused by an acute neuropathy such as Guillain-Barré syndrome, transverse myelitis, a neurotoxin, or a neurotropic viral infection such as poliomyelitis or West Nile virus. When acute weakness is associated with very high levels of serum creatine kinase (CK) (often in the thousands), painful muscle cramps, rhabdomyolysis, and myoglobinuria, it may be due to a viral infection or a metabolic disorder such as myophosphorylase deficiency or carnitine palmitoyltransferase deficiency. Several animal parasites, including protozoa (*Toxoplasma*, *Trypanosoma*), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as *parasitic polymyositis*. *Staphylococcus aureus*, *Yersinia*, *Streptococcus*, or anaerobic bacteria may produce a suppurative myositis, known as *tropical polymyositis*, or *pyomyositis*. Pyomyositis, previously rare in the west, is now occasionally seen in AIDS patients. Other bacteria, such as *Borrelia burgdorferi* (Lyme disease) and *Legionella pneumophila* (Legionnaire's disease), may infrequently cause myositis.

Patients with periodic paralysis experience recurrent episodes of acute muscle weakness without pain, always beginning in childhood. Chronic alcoholics may develop painful myopathy with myoglobinuria after a bout of heavy drinking. Acute painless muscle weakness with myoglobinuria may occur with prolonged hypokalemia, or hypophosphatemia and hypomagnesemia, usually in chronic alcoholics or in patients on nasogastric suction receiving parenteral hyperalimentation.

Myofasciitis

This distinctive inflammatory disorder affecting muscle and fascia presents as diffuse myalgias, skin induration, fatigue, and mild muscle weakness; mild elevations of serum CK are usually present. The most common form is eosinophilic myofasciitis characterized by peripheral blood eosinophilia and eosinophilic infiltrates in the endomysial tissue. In some patients, the eosinophilic myositis/fasciitis occurs in the context of parasitic infections, vasculitis, mixed connective tissue disease, hypereosinophilic syndrome, or toxic exposures (e.g., toxic oil syndrome, contaminated L-tryptophan) or with mutations in the calpain gene. A distinct subset of myofasciitis is characterized by pronounced infiltration of the connective tissue around the muscle by sheets of periodic acid–Schiff-positive macrophages and occasional CD8 T cells (macrophagic myofasciitis). Such histologic involvement is focal and limited to sites of previous vaccinations, which may have been administered months or years earlier. This disorder, which to date has not been observed outside of France, has been linked to an aluminum-containing substrate in vaccines. Most patients respond to glucocorticoid therapy, and the overall prognosis seems favorable.

Necrotizing myositis

This is an increasingly recognized entity that has distinct features, even though it is often labeled as PM. It presents often in the fall or winter as an acute or subacute onset of symmetric muscle weakness; CK is typically extremely high. The weakness can be severe. Coexisting interstitial lung disease and cardiomyopathy may be present. The disorder may develop after a viral infection or in association with cancer. Some patients have antibodies against signal recognition particle (SRP). The muscle biopsy demonstrates necrotic fibers infiltrated by macrophages but only rare, if any, T cell infiltrates. Muscle MHC-I expression is only slightly and focally upregulated. The capillaries may be swollen with hyalinization, thickening of the capillary wall, and deposition of complement. Some patients respond to immunotherapy, but others are resistant.

Hyperacute necrotizing fasciitis/myositis (flesh-eating disease)

This a fulminant infectious disease, seen most often in the tropics or in conditions with poor hygiene, characterized by widespread necrosis of the superficial fascia and muscle of a limb; if the scrotum, perineum, and abdominal wall are affected, the condition is referred to as Fournier's gangrene. It may be caused by group A β-hemolytic streptococcus, methicillin-sensitive *S. aureus*, *Pseudomonas aeruginosa*, *Vibrio vulnificus*, clostridial species (gas gangrene), or polymicrobial infection with anaerobes and facultative bacteria; toxins from these bacteria may act as superantigens (Chap. 1). The port of bacterial entry is usually a trivial cut or skin abrasion and the source is contact with carriers of the organism. Individuals with diabetes mellitus, immunodeficiency states, or systemic illnesses such as liver failure are most susceptible. Systemic varicella is a predisposing factor in children.

The disease presents with swelling, pain, and redness in the involved area followed by a rapid tissue necrosis of fascia and muscle that progresses at an estimated rate of 3 cm/h. Emergency debridement, antibiotics, as well as IVIg, or even hyperbaric oxygen have been recommended. In progressive or advanced cases, amputation of the affected limb may be necessary to avoid a fatal outcome.

Drug-induced myopathies

D-Penicillamine, procainamide, and statins may produce a true myositis resembling PM, and a DM-like illness had been associated with the contaminated preparations of

L-tryptophan. As noted earlier, AZT causes a mitochondrial myopathy. Other drugs may elicit a toxic noninflammatory myopathy that is histologically different from DM, PM, or IBM. These include cholesterol-lowering agents such as clofibrate, lovastatin, simvastatin, or provastatin, especially when combined with cyclosporine, amiodarone, or gemfibrozil. Statin-induced necrotizing myopathy or asymptomatic elevations of CK usually improve after discontinuation of the drug. In rare patients, however, muscle weakness continues to progress even after the statin is withdrawn; in these cases, a diagnostic muscle biopsy is indicated, and if evidence of inflammation and MHC-I upregulation is present, immunotherapy for PM should be considered. Rhabdomyolysis and myoglobinuria have been rarely associated with amphotericin B, ε-aminocaproic acid, fenfluramine, heroin, and phencyclidine. The use of amiodarone, chloroquine, colchicine, carbimazole, emetine, etretinate, ipecac syrup, chronic laxative or licorice use resulting in hypokalemia, and glucocorticoids or growth hormone administration have also been associated with myopathic muscle weakness. Some neuromuscular blocking agents such as pancuronium, in combination with glucocorticoids, may cause an acute critical illness myopathy. A careful drug history is essential for diagnosis of these drug-induced myopathies, which do not require immunosuppressive therapy except when an autoimmune myopathy has been triggered, as noted earlier.

"Weakness" due to muscle pain and muscle tenderness

A number of conditions including *polymyalgia rheumatica* (Chap. 11) and arthritic disorders of adjacent joints may enter into the differential diagnosis of inflammatory myopathy, even though they do not cause myositis. The muscle biopsy is either normal or discloses type II muscle fiber atrophy. Patients with *fibrositis* and *fibromyalgia* (Chap. 22) complain of focal or diffuse muscle tenderness, fatigue, and aching, which is sometimes poorly differentiated from joint pain. Some patients, however, have muscle tenderness, painful muscles on movement, and signs suggestive of a collagen vascular disorder, such as an increased erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, or rheumatoid factor, along with modest elevation of the serum CK and aldolase. They demonstrate a "break-away" pattern of weakness with difficulty sustaining effort, but not true muscle weakness. The muscle biopsy is usually normal or nonspecific. Many such patients show some response to nonsteroidal anti-inflammatory agents or glucocorticoids, though most continue to have indolent complaints. An indolent fasciitis in the setting of an ill-defined connective tissue disorder may be present, and these patients should not be labeled as having a psychosomatic disorder. *Chronic fatigue syndrome*, which may follow a viral infection, can present with debilitating fatigue, fever, sore throat, painful lymphadenopathy, myalgia, arthralgia, sleep disorder, and headache. These patients do not have muscle weakness, and the muscle biopsy is normal.

DIAGNOSIS

The clinically suspected diagnosis of PM, DM, or IBM is confirmed by analysis of serum muscle enzymes, EMG findings, and muscle biopsy **(Table 17-2)**.

The most sensitive enzyme is CK, which in active disease can be elevated as much as fiftyfold. Although the CK level usually parallels disease activity, it can be normal in some patients with active IBM or DM, especially when associated with a connective tissue disease. The CK is always elevated in patients with active PM. Along with the CK, the serum glutamic-oxaloacetic and glutamate pyruvate transaminases, lactate dehydrogenase, and aldolase may be elevated.

Needle EMG shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed potentials (polyphasic units of short and long duration) indicating a chronic process and muscle fiber regeneration are often present in IBM. These EMG findings are not diagnostic of an inflammatory myopathy, but are useful to identify the presence of active or chronic myopathy and to exclude neurogenic disorders.

MRI is not routinely used for the diagnosis of PM, DM, or IBM. However, it may provide information or guide the location of the muscle biopsy in certain clinical settings.

Muscle biopsy—in spite of occasional variability in demonstrating all of the typical pathologic findings—is the most sensitive and specific test for establishing the diagnosis of inflammatory myopathy and for excluding other neuromuscular diseases. Inflammation is the histologic hallmark for these diseases; however, additional features are characteristic of each subtype **(Figs. 17-3, 17-4,** and **17-5)**.

In PM the inflammation is *primary*, a term used to indicate that the inflammation is not reactive and the T cell infiltrates, located primarily within the muscle fascicles (endomysially), surround individual, healthy muscle fibers and result in phagocytosis and necrosis (Fig. 17-3). The MHC-I molecule is ubiquitously expressed on the sarcolemma, even in fibers not invaded by CD8+ cells. The CD8/MHC-I lesion is characteristic and essential to confirm or establish the diagnosis and to exclude disorders with secondary, nonspecific, inflammation, such as in some muscular dystrophies. When the

TABLE 17-2

CRITERIA FOR DIAGNOSIS OF INFLAMMATORY MYOPATHIES

CRITERION	POLYMYOSITIS		DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
	DEFINITE	PROBABLE		
Myopathic muscle weakness[a]	Yes	Yes	Yes[b]	Yes; slow onset, early involvement of distal muscles, frequent falls
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to fiftyfold)	Elevated (up to fiftyfold)	Elevated (up to fiftyfold) or normal	Elevated (up to tenfold) or normal
Muscle biopsy findings[c]	"Primary" inflammation with the CD8/MHC-I complex and no vacuoles	Ubiquitous MHC-I expression but minimal inflammation and no vacuoles[d]	Perifascicular, perimysial, or perivascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/MHC-I complex; vacuolated fibers with β-amyloid deposits; cytochrome oxygenase–negative fibers; signs of chronic myopathy[e]
Rash or calcinosis	Absent	Absent	Present[f]	Absent

[a]Myopathic muscle weakness, affecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterized by a subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no endocrinopathy, no exposure to myotoxic drugs or toxins, and no biochemical muscle disease (excluded on the basis of muscle-biopsy findings).
[b]In some cases with the typical rash, the muscle strength is seemingly normal (dermatomyositis sine myositis); these patients often have new onset of easy fatigue and reduced endurance. Careful muscle testing may reveal mild muscle weakness.
[c]See text for details.
[d]An adequate trial of prednisone or other immunosuppressive drugs is warranted in probable cases. If, in retrospect, the disease is unresponsive to therapy, another muscle biopsy should be considered to exclude other diseases or possible evolution in inclusion body myositis.
[e]If the muscle biopsy does not contain vacuolated fibers but shows chronic myopathy with hypertrophic fibers, primary inflammation with the CD8/MHC-I complex and cytochrome oxygenase–negative fibers, the diagnosis is probable inclusion body myositis.
[f]If rash is absent but muscle biopsy findings are characteristic of dermatomyositis, the diagnosis is probable dermatomyositis.

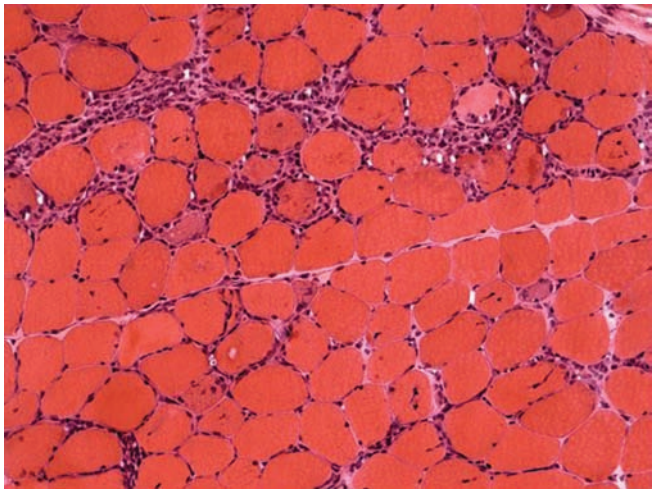


FIGURE 17-3

Cross-section of a muscle biopsy from a patient with polymyositis demonstrates scattered inflammatory foci with lymphocytes invading or surrounding muscle fibers. Note lack of chronic myopathic features (increased connective tissue, atrophic or hypertrophic fibers) as seen in inclusion body myositis.

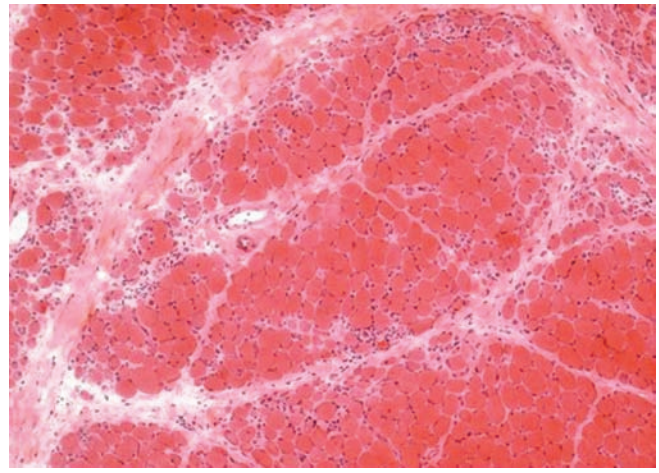


FIGURE 17-4

Cross-section of a muscle biopsy from a patient with dermatomyositis demonstrates atrophy of the fibers at the periphery of the fascicle (perifascicular atrophy).

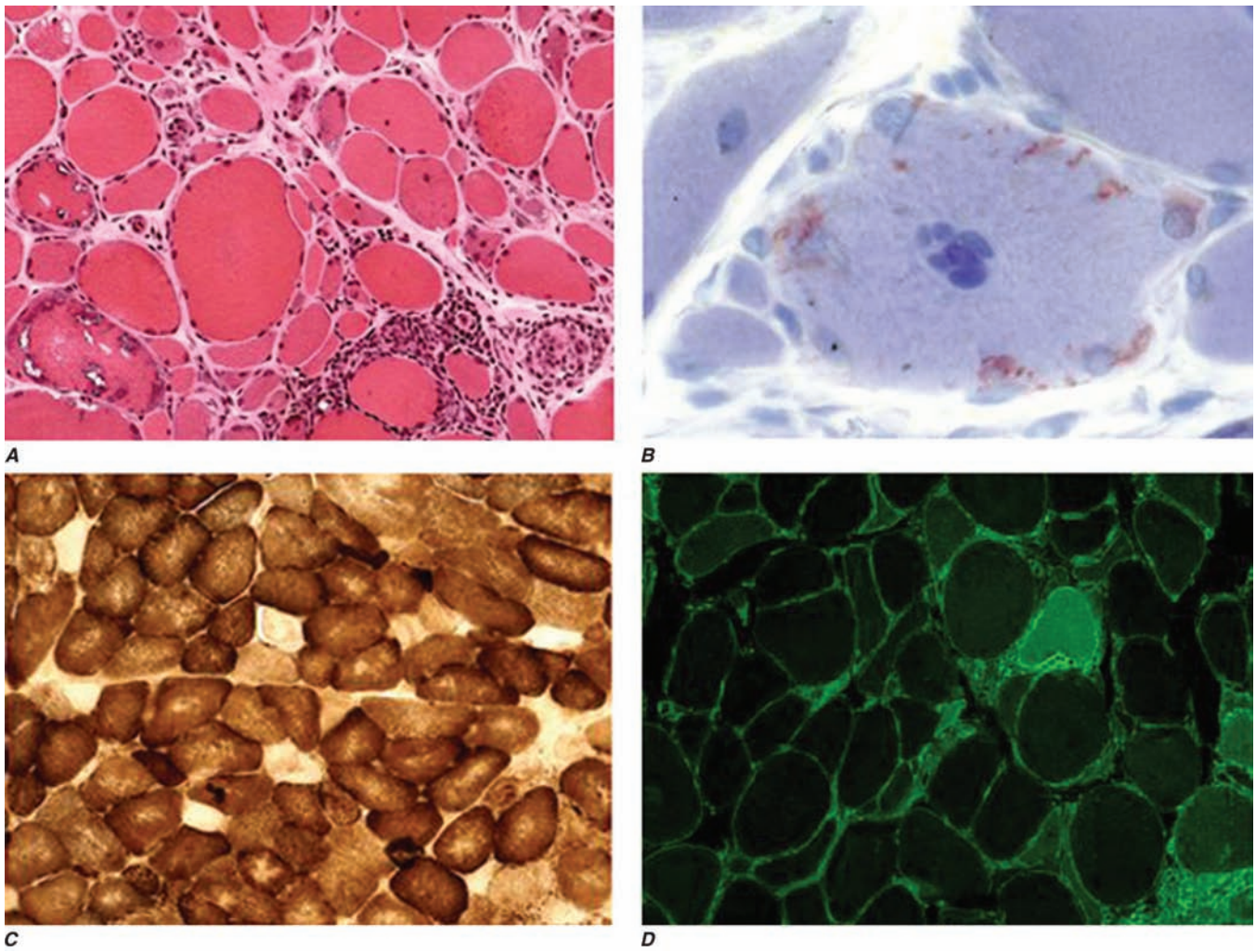


FIGURE 17-5

Cross-sections of a muscle biopsy from a patient with inclusion body myositis demonstrate the typical features of vacuoles with lymphocytic infiltrates surrounding nonvacuolated or necrotic fibers (***A***), tiny endomysial deposits of amyloid visualized with crystal violet (***B***), cytochrome oxidase–negative fibers, indicative of mitochondrial dysfunction (***C***), and ubiquitous MHC-I expression at the periphery of all fibers (***D***).

disease is chronic, connective tissue is increased and may react positively with alkaline phosphatase.

In DM the endomysial inflammation is predominantly perivascular or in the interfascicular septae and around—rather than within—the muscle fascicles (Fig. 17-4). The intramuscular blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi, and obliteration of capillaries. The muscle fibers undergo necrosis, degeneration, and phagocytosis, often in groups involving a portion of a muscle fasciculus in a wedgelike shape or at the periphery of the fascicle, due to microinfarcts within the muscle. This results in perifascicular atrophy, characterized by 2–10 layers of atrophic fibers at the periphery of the fascicles. The presence of perifascicular atrophy is diagnostic of DM, *even in the absence of inflammation*.

In IBM (Fig. 17-5), there is endomysial inflammation with T cells invading MHC-I-expressing nonvacuolated muscle fibers; basophilic granular deposits distributed around the edge of slitlike vacuoles (rimmed vacuoles); loss of fibers, replaced by fat and connective tissue, hypertrophic fibers, and angulated or round fibers; rare eosinophilic cytoplasmic inclusions; abnormal mitochondria characterized by the presence of ragged-red fibers or cytochrome oxidase–negative fibers; and amyloid deposits within or next to the vacuoles best visualized with crystal violet or Congo-red staining viewed with fluorescent optics. Electron microscopy demonstrates filamentous inclusions in the vicinity of the rimmed vacuoles. In at least 15% of patients with the typical clinical phenotype of IBM, no vacuoles or amyloid deposits can be identified in muscle biopsy, leading to

an erroneous diagnosis of PM. Close clinicopathologic correlations are essential; if uncertain, a repeat muscle biopsy from another site is often helpful.

TREATMENT Therapy of Inflammatory Myopathies

The goal of therapy is to improve muscle strength, thereby improving function in activities of daily living, and ameliorate the extramuscular manifestations (rash, dysphagia, dyspnea, fever). When strength improves, the serum CK falls concurrently; however, the reverse is not always true. Unfortunately, there is a common tendency to "chase" or treat the CK level instead of the muscle weakness, a practice that has led to prolonged and unnecessary use of immunosuppressive drugs and erroneous assessment of their efficacy. It is prudent to discontinue these drugs if, after an adequate trial, there is no objective improvement in muscle strength whether or not CK levels are reduced. Agents used in the treatment of PM and DM include the following:

1. *Glucocorticoids*. Oral prednisone is the initial treatment of choice; the effectiveness and side effects of this therapy determine the future need for stronger immunosuppressive drugs. High-dose prednisone, at least 1 mg/kg per day, is initiated as early in the disease as possible. After 3–4 weeks, prednisone is tapered slowly over a period of 10 weeks to 1 mg/kg every other day. If there is evidence of efficacy and no serious side effects, the dosage is then further reduced by 5 or 10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. The efficacy of prednisone is determined by an objective increase in muscle strength and activities of daily living, which almost always occurs by the third month of therapy. A feeling of increased energy or a reduction of the CK level without a concomitant increase in muscle strength is not a reliable sign of improvement. If prednisone provides no objective benefit after ~3 months of high-dose therapy, the disease is probably unresponsive to the drug and tapering should be accelerated while the next-in-line immunosuppressive drug is started. Although controlled trials have not been performed, almost all patients with true PM or DM respond to glucocorticoids to *some degree and for some period of time*; in general, DM responds better than PM.

 The long-term use of prednisone may cause increased weakness associated with a normal or unchanged CK level; this effect is referred to as *steroid myopathy*. In a patient who previously responded to high doses of prednisone, the development of new weakness may be related to steroid myopathy or to disease activity that either will respond to a higher dose of glucocorticoids or has become glucocorticoid-resistant. In uncertain cases, the prednisone dosage can be steadily increased or decreased as desired: the cause of the weakness is usually evident in 2–8 weeks.
2. *Other immunosuppressive drugs*. Approximately 75% of patients ultimately require additional treatment. This occurs when a patient fails to respond adequately to glucocorticoids after a 3-month trial, the patient becomes glucocorticoid-resistant, glucocorticoid-related side effects appear, attempts to lower the prednisone dose repeatedly result in a new relapse, or rapidly progressive disease with evolving severe weakness and respiratory failure develops.

 The following drugs are commonly used but have never been tested in controlled studies: (1) *Azathioprine* is well tolerated, has few side effects, and appears to be as effective for long-term therapy as other drugs. The dose is up to 3 mg/kg daily. (2) *Methotrexate* has a faster onset of action than azathioprine. It is given orally starting at 7.5 mg weekly for the first 3 weeks (2.5 mg every 12 h for 3 doses), with gradual dose escalation by 2.5 mg per week to a total of 25 mg weekly. A rare side effect is methotrexate pneumonitis, which can be difficult to distinguish from the interstitial lung disease of the primary myopathy associated with Jo-1 antibodies (described earlier). (3) *Mycophenolate mofetil* also has a faster onset of action than azathioprine. At doses up to 2.5 or 3 gm/d in two divided doses, it is well tolerated for long-term use. (4) Monoclonal anti-CD20 antibody (rituximab) has been shown in a small uncontrolled series to benefit patients with DM and PM and is currently being investigated in a randomized trial. (5) *Cyclosporine* has inconsistent and mild benefit. (6) *Cyclophosphamide* (0.5–1 g/m^2 IV monthly for 6 months) has limited success and significant toxicity. (7) Tacrolimus (formerly known as Fk506) has been effective in some difficult cases of PM.
3. *Immunomodulation*. In a controlled trial of patients with refractory DM, intravenous immunoglobulin (IVIg) improved not only strength and rash but also the underlying immunopathology. The benefit is often short-lived (≤8 weeks), and repeated infusions every 6–8 weeks are generally required to maintain improvement. A dose of 2 g/kg divided over 2–5 days per course is recommended. Uncontrolled observations suggest that IVIg may also be beneficial for patients with PM. Neither plasmapheresis nor leukapheresis appears to be effective in PM and DM.

The following sequential empirical approach to the treatment of PM and DM is suggested: *Step 1*: high-dose prednisone; *Step 2*: azathioprine, mycophenolate, or methotrexate for steroid-sparing effect; *Step 3*: IVIg;

Step 4: a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug, and general health: rituximab, cyclosporine, cyclophosphamide, or tacrolimus. Patients with interstitial lung disease may benefit from aggressive treatment with cyclophosphamide or tacrolimus.

A patient with presumed PM who has not responded to any form of immunotherapy most likely has IBM or another disease, usually a metabolic myopathy, a muscular dystrophy, a drug-induced myopathy, or an endocrinopathy. In these cases, a repeat muscle biopsy and a renewed search for another cause of the myopathy is indicated.

Calcinosis, a manifestation of DM, is difficult to treat; however, new calcium deposits may be prevented if the primary disease responds to the available therapies. Bisphosphonates, aluminum hydroxide, probenecid, colchicine, low doses of warfarin, calcium blockers, and surgical excision have all been tried without success.

IBM is generally resistant to immunosuppressive therapies. Prednisone together with azathioprine or methotrexate is often tried for a few months in newly diagnosed patients, although results are generally disappointing. Because occasional patients may feel subjectively weaker after these drugs are discontinued, some clinicians prefer to maintain these patients on low-dose, every-other-day prednisone along with mycophenolate in an effort to slow disease progression, even though there is no objective evidence or controlled study to support this practice. In two controlled studies of IVIg in IBM, minimal benefit in up to 30% of patients was found; the strength gains, however, were not of sufficient magnitude to justify its routine use. Another trial of IVIg combined with prednisone was ineffective. Nonetheless, many experts believe that a 2- to 3-month trial with IVIg may be reasonable for selected patients with IBM who experience rapid progression of muscle weakness or choking episodes due to worsening dysphagia.

PROGNOSIS

The 5-year survival rate for treated patients with PM and DM is ~95% and the 10-year survival rate is 84%; death is usually due to pulmonary, cardiac, or other systemic complications. The prognosis is worse for patients who are severely affected at presentation, when initial treatment is delayed, and in cases with severe dysphagia or respiratory difficulties. Older patients, and those with associated cancer also have a worse prognosis. DM responds more favorably to therapy than PM and, thus, has a better prognosis. Most patients improve with therapy, and many make a full functional recovery, which is often sustained with maintenance therapy. Up to 30% may be left with some residual muscle weakness. Relapses may occur at any time.

IBM has the least favorable prognosis of the inflammatory myopathies. Most patients will require the use of an assistive device such as a cane, walker, or wheelchair within 5–10 years of onset. In general, the older the age of onset in IBM, the more rapidly progressive is the course.

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SECTION III

DISORDERS OF THE JOINTS AND ADJACENT TISSUES

CHAPTER 18

APPROACH TO ARTICULAR AND MUSCULOSKELETAL DISORDERS

John J. Cush ■ Peter E. Lipsky

Musculoskeletal complaints account for >315 million outpatient visits per year and nearly 20% of all outpatient visits in the United States. The Centers for Disease Control and Prevention estimate that 22% (46 million) of the U.S. population has physician-diagnosed arthritis and 19 million have significant functional limitation. While many patients will have self-limited conditions requiring minimal evaluation and only symptomatic therapy and reassurance, specific musculoskeletal presentations or their persistence may herald a more serious condition that requires further evaluation or laboratory testing to establish a diagnosis. The goal of the musculoskeletal evaluation is to formulate a differential diagnosis that leads to an accurate diagnosis and timely therapy, while avoiding excessive diagnostic testing and unnecessary treatment **(Table 18-1)**. There are several urgent conditions that must be diagnosed promptly to avoid significant morbid or mortal sequelae. These "red flag" diagnoses include septic arthritis, acute crystal-induced arthritis (e.g., gout), and fracture. Each may be suspected by its acute onset and monarticular or focal musculoskeletal pain (see later in chapter).

TABLE 18-1

EVALUATION OF PATIENTS WITH MUSCULOSKELETAL COMPLAINTS

- Goals
 - Accurate diagnosis
 - Timely provision of therapy
 - Avoidance of unnecessary diagnostic testing
- Approach
 - Anatomic localization of complaint (articular vs. nonarticular)
 - Determination of the nature of the pathologic process (inflammatory vs. noninflammatory)
 - Determination of the extent of involvement (monarticular, polyarticular, focal, widespread)
 - Determination of chronology (acute vs. chronic)
 - Consider the most common disorders first
 - Formulation of a differential diagnosis

Individuals with musculoskeletal complaints should be evaluated with a thorough history, a comprehensive physical and musculoskeletal examination, and, if appropriate, laboratory testing. The initial encounter should determine whether the musculoskeletal complaint signals a red flag condition (septic arthritis, gout, or fracture) or not. The evaluation should proceed to ascertain if the complaint is (1) *articular* or *nonarticular* in origin, (2) *inflammatory* or *noninflammatory* in nature, (3) *acute* or *chronic* in duration, and (4) *localized (monarticular)* or *widespread* (*polyarticular*) in distribution.

With such an approach and an understanding of the pathophysiologic processes, the musculoskeletal complaint or presentation can be characterized (e.g., acute inflammatory monarthritis or a chronic noninflammatory, nonarticular widespread pain) to narrow the diagnostic possibilities. A diagnosis can be made in the vast majority of individuals. However, some patients will not fit immediately into an established diagnostic category. Many musculoskeletal disorders resemble each other at the outset, and some may take weeks or months to evolve into a readily recognizable diagnostic entity. This consideration should temper the desire to establish a definitive diagnosis at the first encounter.

ARTICULAR VERSUS NONARTICULAR

The musculoskeletal evaluation must discriminate the anatomic origin(s) of the patient's complaint. For example, ankle pain can result from a variety of pathologic conditions involving disparate anatomic structures, including gonococcal arthritis, calcaneal fracture, Achilles tendinitis, plantar fasciitis, cellulitis, and peripheral or entrapment neuropathy. Distinguishing between

articular and nonarticular conditions requires a careful and detailed examination. Articular structures include the synovium, synovial fluid, articular cartilage, intraarticular ligaments, joint capsule, and juxtaarticular bone. Nonarticular (or periarticular) structures, such as supportive extraarticular ligaments, tendons, bursae, muscle, fascia, bone, nerve, and overlying skin, may be involved in the pathologic process. Although musculoskeletal complaints are often ascribed to the joints, nonarticular disorders more frequently underlie such complaints. Distinguishing between these potential sources of pain may be challenging to the unskilled examiner. Articular disorders may be characterized by deep or diffuse pain, pain or limited range of motion on active and passive movement, and swelling (caused by synovial proliferation, effusion, or bony enlargement), crepitation, instability, "locking," or deformity. By contrast, nonarticular disorders tend to be painful on active, but not passive (or assisted), range of motion. Periarticular conditions often demonstrate point or focal tenderness in regions adjacent to articular structures, and have physical findings remote from the joint capsule. Moreover, nonarticular disorders seldom demonstrate swelling, crepitus, instability, or deformity of the joint itself.

INFLAMMATORY VERSUS NONINFLAMMATORY DISORDERS

In the course of a musculoskeletal evaluation, the examiner should determine the nature of the underlying pathologic process and whether inflammatory or noninflammatory findings exist. Inflammatory disorders may be infectious (infection with *Neisseria gonorrhoea* or *Mycobacterium tuberculosis*), crystal-induced (gout, pseudogout), immune-related (rheumatoid arthritis [RA], systemic lupus erythematosus [SLE]), reactive (rheumatic fever, reactive arthritis), or idiopathic. Inflammatory disorders may be identified by any of the four cardinal signs of inflammation (erythema, warmth, pain, or swelling), systemic symptoms (fatigue, fever, rash, weight loss), or laboratory evidence of inflammation (elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP], thrombocytosis, anemia of chronic disease, or hypoalbuminemia). Articular stiffness commonly accompanies chronic musculoskeletal disorders and can extend beyond the joint. However, the severity and duration of stiffness may be diagnostically important. Morning stiffness related to inflammatory disorders (such as RA or polymyalgia rheumatica) is precipitated by prolonged rest, is described as severe, lasts for hours, and may improve with activity or anti-inflammatory medications. By contrast, intermittent stiffness (also known as gel phenomenon), associated with noninflammatory conditions (such as osteoarthritis [OA]), is precipitated by brief periods of rest, usually lasts less than 60 minutes, and is exacerbated by activity. Fatigue may accompany inflammation (as seen in RA and polymyalgia rheumatica), but may also be a consequence of fibromyalgia (a noninflammatory disorder), anemia, cardiac failure, endocrinopathy, poor nutrition, chronic pain, poor sleep, or depression. Noninflammatory disorders may be related to trauma (rotator cuff tear), repetitive use (bursitis, tendinitis), degeneration or ineffective repair (OA), neoplasm (pigmented villonodular synovitis), or pain amplification (fibromyalgia). Noninflammatory disorders are often characterized by pain without synovial swelling or warmth, absence of inflammatory or systemic features, daytime gel phenomena rather than morning stiffness, and normal (for age) or negative laboratory investigations.

Identification of the nature of the underlying process and the site of the complaint will enable the examiner to characterize the musculoskeletal presentation (e.g., acute inflammatory monarthritis, chronic noninflammatory, nonarticular widespread pain), narrow the diagnostic considerations, and assess the need for immediate diagnostic or therapeutic intervention or for continued observation. **Figure 18-1** presents an algorithmic approach to the evaluation of patients with musculoskeletal complaints. This approach is remarkably effective and relies on clinical and historic features, rather than laboratory testing, to diagnose many common rheumatic disorders.

The algorithmic approach may be unnecessary in patients with the most commonly encountered ailments; as these can also be considered based on frequency and characteristic presentations. The most prevalent causes of musculoskeletal complaints are shown in **Fig. 18-2**. As trauma, fracture, overuse syndromes, and fibromyalgia are among the most common causes of presentation, these should be considered during the initial encounter. If these possibilities are excluded, other frequently occurring disorders should be considered according to the patient's age. Hence, those younger than 60 years are commonly affected by repetitive use/strain disorders, gout (men only), RA, spondyloarthritis, and uncommonly, infectious arthritis. Patients over age 60 years are frequently affected by OA, crystal (gout and pseudogout) arthritis, polymyalgia rheumatica, osteoporotic fracture, and uncommonly, septic arthritis. These conditions are between 10 and 100 times more prevalent than other serious autoimmune conditions, such as systemic lupus erythematosus, scleroderma, polymyositis, and vasculitis.

CLINICAL HISTORY

Additional historic features may reveal important clues to the diagnosis. Aspects of the patient profile,

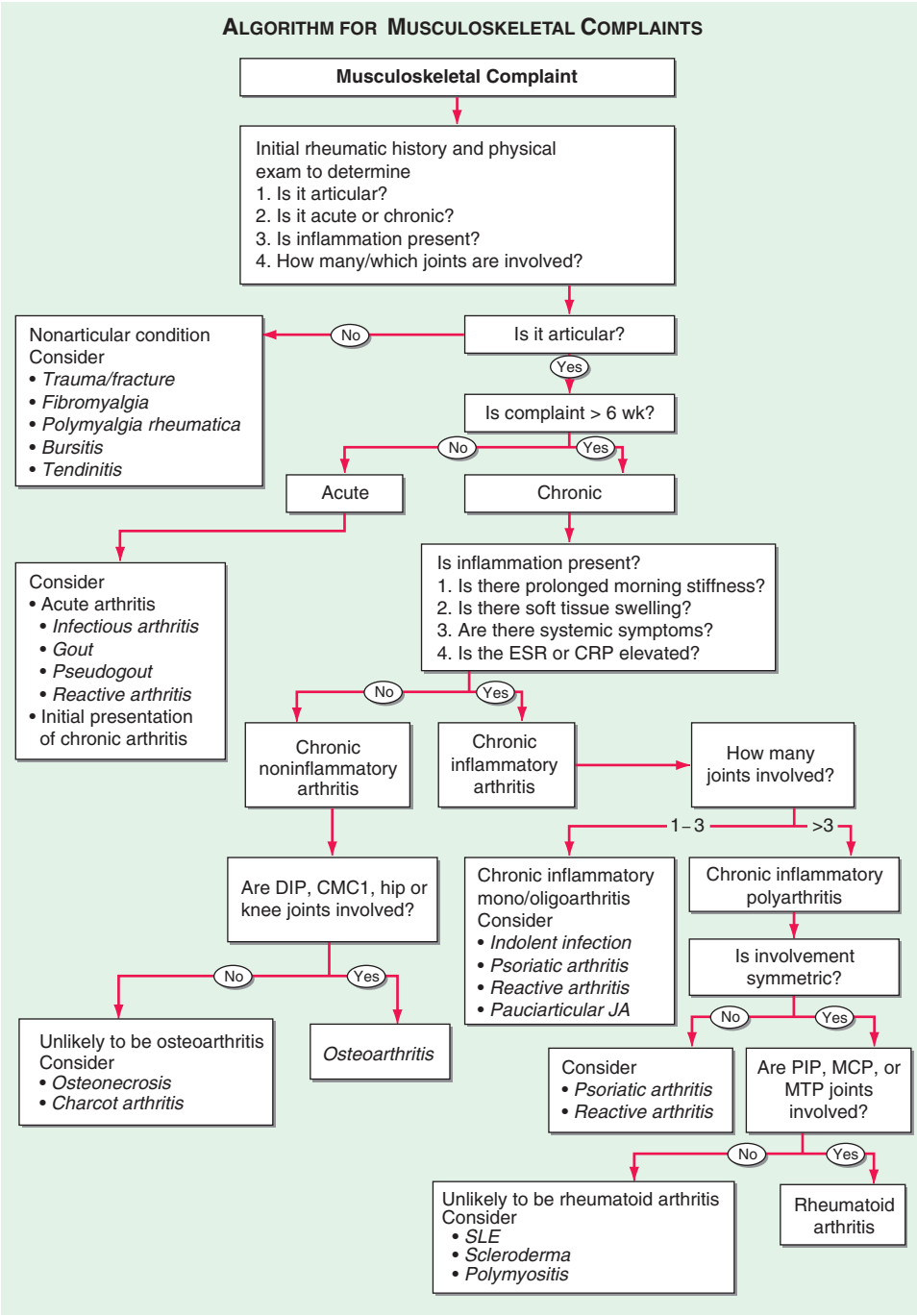


FIGURE 18-1
Algorithm for the diagnosis of musculoskeletal complaints. An approach to formulating a differential diagnosis (shown in italics). CMC, carpometacarpal; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; JA, juvenile arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus.

complaint chronology, extent of joint involvement, and precipitating factors can provide important information. Certain diagnoses are more frequent in different *age* groups (Fig. 18-2). SLE and reactive arthritis occur more frequently in the young, whereas fibromyalgia and RA are frequent in middle age, and OA and polymyalgia rheumatica are more prevalent among the elderly. Diagnostic clustering is also evident when *sex* and *race* are considered. Gout and the spondyloarthropathies (e.g., ankylosing spondylitis) are more common in men, whereas RA, fibromyalgia, and lupus are more frequent in women. *Racial predilections* may be evident. Thus, polymyalgia rheumatica, giant cell arteritis, and granulomatosis with polyangiitis (Wegener's) commonly affect whites, whereas sarcoidosis and SLE more commonly affect African Americans. *Familial aggregation* may be seen in disorders such as ankylosing spondylitis, gout, and Heberden's nodes of OA.

The chronology of the complaint is an important diagnostic feature and can be divided into the *onset*, *evolution*, and *duration*. The onset of disorders such as septic arthritis or gout tends to be abrupt, whereas OA, RA, and fibromyalgia may have more indolent presentations. The patients' complaints may evolve differently

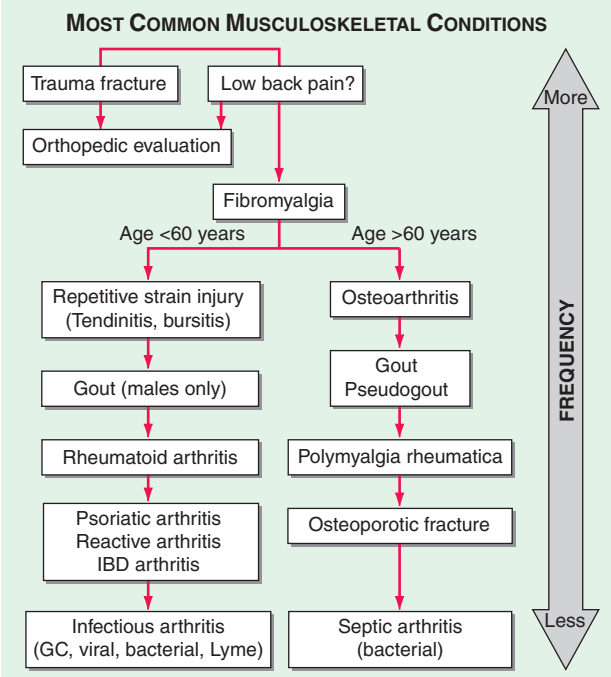


FIGURE 18-2

Algorithm for consideration of the most common musculoskeletal conditions. GC, gonococcal; IBD, inflammatory bowel disease.

and be classified as chronic (OA), intermittent (crystal or Lyme arthritis), migratory (rheumatic fever, gonococcal or viral arthritis), or additive (RA, psoriatic arthritis). Musculoskeletal disorders are typically classified as acute or chronic based upon a symptom duration that is either less than or greater than 6 weeks, respectively. Acute arthropathies tend to be infectious, crystal-induced, or reactive. Chronic conditions include noninflammatory or immunologic arthritides (e.g., OA, RA) and nonarticular disorders (e.g., fibromyalgia).

The *extent* or *distribution* of articular involvement is often informative. Articular disorders are classified based on the number of joints involved, as either *monarticular* (one joint), *oligoarticular* or *pauciarticular* (two or three joints), or *polyarticular* (four or more joints). Although crystal and infectious arthritis are often mono- or oligoarticular, OA and RA are polyarticular disorders. Nonarticular disorders may be classified as either focal or widespread. Complaints secondary to tendinitis or carpal tunnel syndrome are typically focal, whereas weakness and myalgia, caused by polymyositis or fibromyalgia, are more diffuse in their presentation. Joint involvement in RA tends to be symmetric, whereas the spondyloarthropathies and gout are often asymmetric and oligoarticular. The upper extremities are frequently involved in RA and OA, whereas lower extremity arthritis is characteristic of reactive arthritis and gout at their onset. Involvement of the axial skeleton is common in OA and ankylosing spondylitis but is infrequent in RA, with the notable exception of the cervical spine.

The clinical history should also identify *precipitating events*, such as trauma (osteonecrosis, meniscal tear), drug administration **(Table 18-2)**, or antecedent or intercurrent illnesses (rheumatic fever, reactive arthritis, hepatitis), that may have contributed to the patient's complaint. Certain comorbidities may predispose to musculoskeletal consequences. This is especially so for diabetes mellitus (carpal tunnel syndrome), renal insufficiency (gout), psoriasis (psoriatic arthritis), myeloma (low back pain), cancer (myositis), and osteoporosis (fracture) or when using certain drugs such as glucocorticoids (osteonecrosis, septic arthritis) and diuretics or chemotherapy (gout) (Table 18-2).

Lastly, a thorough *rheumatic review of systems* may disclose useful diagnostic information. A variety of musculoskeletal disorders may be associated with systemic features such as fever (SLE, infection), rash

TABLE 18-2

DRUG-INDUCED MUSCULOSKELETAL CONDITIONS

Arthralgias	Quinidine, cimetidine, quinolones, chronic acyclovir, interferon, IL-2, nicardipine, vaccines, rifabutin, aromatase and HIV protease inhibitors
Myalgias/myopathy	Glucocorticoids, penicillamine, hydroxychloroquine, AZT, lovastatin, simvastatin, pravastatin, clofibrate, interferon, IL-2, alcohol, cocaine, taxol, docetaxel, colchicine, quinolones, cyclosporine, protease inhibitors
Tendon rupture/tendinitis	Quinolones, glucocorticoids, isotretinoin
Gout	Diuretics, aspirin, cytotoxics, cyclosporine, alcohol, moonshine, ethambutol
Drug-induced lupus	Hydralazine, procainamide, quinidine, phenytoin, carbamazepine, methyldopa, isoniazid, chlorpromazine, lithium, penicillamine, tetracyclines, TNF inhibitors, ACE inhibitors, ticlopidine
Osteonecrosis	Glucocorticoids, alcohol, radiation, bisphosphonates
Osteopenia	Glucocorticoids, chronic heparin, phenytoin, methotrexate
Scleroderma	Vinyl chloride, bleomycin, pentazocine, organic solvents, carbidopa, tryptophan, rapeseed oil
Vasculitis	Allopurinol, amphetamines, cocaine, thiazides, penicillamine, propylthiouracil, montelukast, TNF inhibitors, hepatitis B vaccine, trimethoprim/sulfamethoxazole

Abbreviations: ACE, angiotensin-converting enzyme; IL-2, interleukin 2; TNF, tumor necrosis factor.

(SLE, psoriatic arthritis), nail abnormalities (psoriatic or reactive arthritis), myalgias (fibromyalgia, statin- or drug-induced myopathy), or weakness (polymyositis, neuropathy). In addition, some conditions are associated with involvement of other organ systems including the eyes (Behçet's disease, sarcoidosis, spondyloarthritis), gastrointestinal tract (scleroderma, inflammatory bowel disease), genitourinary tract (reactive arthritis, gonococcemia), or the nervous system (Lyme disease, vasculitis).

RHEUMATOLOGIC EVALUATION OF THE ELDERLY

The incidence of rheumatic diseases rises with age, such that 58% of those >65 years will have joint complaints. Musculoskeletal disorders in elderly patients are often not diagnosed because the signs and symptoms may be insidious, overlooked, or overshadowed by comorbidities. These difficulties are compounded by the diminished reliability of laboratory testing in the elderly, who often manifest nonpathologic abnormal results. For example, the ESR may be misleadingly elevated, and low-titer positive tests for rheumatoid factor and antinuclear antibodies (ANAs) may be seen in up to 15% of elderly patients. Although nearly all rheumatic disorders afflict the elderly, certain diseases and drug-induced disorders (Table 18-2) are more common in this age group. The elderly should be approached in the same manner as other patients with musculoskeletal complaints, but with an emphasis on identifying the potential rheumatic consequences of medical comorbidities and therapies. OA, osteoporosis, gout, pseudogout, polymyalgia rheumatica, vasculitis, and drug-induced disorders are all more common in the elderly than in other individuals. The physical examination should identify the nature of the musculoskeletal complaint as well as coexisting diseases that may influence diagnosis and choice of treatment.

RHEUMATOLOGIC EVALUATION OF THE HOSPITALIZED PATIENT

Inpatient and outpatient evaluations and diagnostic considerations may differ, owing to greater symptom severity, more acute presentations, and greater interplay of comorbidities with the hospitalized patient. Patients with rheumatic disorders tend to be admitted for one of several reasons: (1) acute onset of inflammatory arthritis; (2) undiagnosed systemic or febrile illness; (3) musculoskeletal trauma; or (4) exacerbation or deterioration of an existing autoimmune disorder (e.g., SLE); or (5) new medical comorbidities (e.g., thrombotic event, lymphoma, infection) arising in patients with articular or connective tissue disorders. Notably, in the United States, rheumatic patients are seldom if ever admitted because of widespread pain, serologic abnormalities, or for the initiation of new therapies, although this is routinely done in other parts of the world.

Acute monarticular inflammatory arthritis may be a "red flag condition" (e.g., septic arthritis, gout, pseudogout) that will require arthrocentesis. However, new-onset polyarticular inflammatory arthritis will have a wider differential diagnosis (e.g., RA, hepatitis-related arthritis, serum sickness, drug-induced lupus, polyarticular septic arthritis) and may require targeted laboratory investigations rather than synovial fluid analysis. Patients with febrile, multisystem disorders will require exclusion of infectious or neoplastic etiologies and an evaluation driven by dominant symptoms with the greatest specificity. Conditions worthy of consideration may include vasculitis (giant cell arteritis in the elderly or polyarteritis nodosa in younger patients), adult-onset Still's disease, SLE, antiphospholipid syndrome, and sarcoidosis. As misdiagnosis of connective tissue disorders is common, patients who present with a reported preexisting rheumatic condition (e.g., SLE, RA, ankylosing spondylitis) should have their diagnosis confirmed by careful history, physicial and musculoskeletal examination, and detailed review of their medical records. It is important to note that when rheumatic disease patients are admitted to the hospital, it is usually for medical problems unrelated to their autoimmune disease, but rather because of either a comorbid condition or complication of drug therapy. Patients with chronic inflammatory disorders (e.g., RA, SLE, psoriasis, etc.) have an augmented risk of infection, cardiovascular events, and neoplasia.

Certain conditions, such as acute gout, can be precipitated in hospitalized patients by surgery, dehydration, or other events and should be considered when hospitalized patients are evaluated for the acute onset of a musculoskeletal condition. It is also common for positive results obtained from overly aggressive and unfocused laboratory testing to generate the need for a full rheumatologic evaluation.

PHYSICAL EXAMINATION

The goal of the physical examination is to ascertain the structures involved, the nature of the underlying pathology, the functional consequences of the process, and the presence of systemic or extraarticular manifestations. A knowledge of topographic anatomy is necessary to identify the primary site(s) of involvement and differentiate articular from nonarticular disorders. The musculoskeletal examination depends largely on careful inspection, palpation, and a variety of specific physical maneuvers to elicit diagnostic signs **(Table 18-3)**.

TABLE 18-3

GLOSSARY OF MUSCULOSKELETAL TERMS
Crepitus A palpable (less commonly audible) vibratory or crackling sensation elicited with joint motion; fine joint crepitus is common and often insignificant in large joints; coarse joint crepitus indicates advanced cartilaginous and degenerative changes (as in osteoarthritis)
Subluxation Alteration of joint alignment such that articulating surfaces incompletely approximate each other
Dislocation Abnormal displacement of articulating surfaces such that the surfaces are not in contact
Range of motion For diarthrodial joints, the arc of measurable movement through which the joint moves in a single plane
Contracture Loss of full movement resulting from a fixed resistance caused either by tonic spasm of muscle (reversible) or by fibrosis of periarticular structures (permanent)
Deformity Abnormal shape or size of a structure; may result from bony hypertrophy, malalignment of articulating structures, or damage to periarticular supportive structures
Enthesitis Inflammation of the entheses (tendinous or ligamentous insertions on bone)
Epicondylitis Infection or inflammation involving an epicondyle

Although most articulations of the appendicular skeleton can be examined in this manner, adequate inspection and palpation are not possible for many axial (e.g., zygapophyseal) and inaccessible (e.g., sacroiliac or hip) joints. For such joints, there is a greater reliance upon specific maneuvers and imaging for assessment.

Examination of involved and uninvolved joints will determine whether *pain*, *warmth*, *erythema*, or *swelling* is present. The locale and level of pain elicited by palpation or movement should be quantified. One example would be to count the number of tender joints on palpation of 28 easily examined joints (proximal interphalangeals [PIPs], metacarpophalangeals [MCPs], wrists, elbows, shoulders, and knees) (with a range of 0–28). Similarly, the number of swollen joints (0–28) can be counted and recorded. Careful examination should distinguish between true articular swelling (caused by synovial effusion or synovial proliferation) and nonarticular (or periarticular) involvement, which usually extends beyond the normal joint margins. Synovial effusion can be distinguished from synovial hypertrophy or bony hypertrophy by palpation or specific maneuvers. For example, small to moderate knee effusions may be identified by the "bulge sign" or "ballottement of the patellae." Bursal effusions (e.g., effusions of the olecranon or prepatellar bursa) are often focal, periarticular, overlie bony prominences, and are fluctuant with sharply defined borders. Joint *stability* can be assessed by palpation and by the application of manual stress. *Subluxation* or *dislocation*, which may be secondary to traumatic, mechanical, or inflammatory causes, can be assessed by inspection and palpation. Joint *swelling or volume* can be assessed by palpation. Distention of the articular capsule usually causes pain and evident swelling. The patient will attempt to minimize the pain by maintaining the joint in the position of least intraarticular pressure and greatest volume, usually partial flexion. For this reason, inflammatory effusions may give rise to flexion contractures. Clinically, this may be detected as fluctuant or "squishy" swelling, with grapelike compressibility. Inflammation may result in fixed flexion deformities, or diminished range of motion—especially on extension, when joint volumes are decreased. Active and passive *range of motion* should be assessed in all planes, with contralateral comparison. Serial evaluations of the joints should record the number of tender and swollen joints and loss of a normal range of motion, using a goniometer to quantify the arc of movement. Each joint should be passively manipulated through its full range of motion (including, as appropriate, flexion, extension, rotation, abduction, adduction, lateral bending, inversion, eversion, supination, pronation, medial/lateral deviation, plantar- or dorsiflexion). Limitation of motion is frequently caused by effusion, pain, deformity, or contracture. If passive motion exceeds active motion, a periarticular process (e.g., tendinitis, tendon rupture, or myopathy) should be considered. *Contractures* may reflect antecedent synovial inflammation or trauma. Minor joint *crepitus* is common during joint palpation and maneuvers, but may indicate significant cartilage degeneration as it becomes coarser (e.g., OA). Joint *deformity* usually indicates a long-standing or aggressive pathologic process. Deformities may result from ligamentous destruction, soft tissue contracture, bony enlargement, ankylosis, erosive disease, or subluxation. Examination of the musculature will document strength, atrophy, pain, or spasm. Appendicular muscle weakness should be characterized as proximal or distal. Muscle strength should be assessed by observing the patient's performance (e.g., walking, rising from a chair, grasping, writing). Strength may also be graded on a 5-point scale: 0 for no movement; 1 for trace movement or twitch; 2 for movement with gravity eliminated; 3 for movement against gravity only; 4 for movement against gravity and resistance; and 5 for normal strength. The examiner should assess for often-overlooked nonarticular or periarticular involvement, especially when articular complaints are not supported by objective findings referable to the joint capsule.

The identification of soft tissue/nonarticular pain will prevent unwarranted and often expensive additional evaluations. Specific maneuvers may reveal common nonarticular abnormalities, such as a carpal tunnel syndrome (which can be identified by Tinel's or Phalen's sign). Other examples of soft tissue abnormalities include olecranon bursitis, epicondylitis (e.g., tennis elbow), enthesitis (e.g., Achilles tendinitis), and tender trigger points associated with fibromyalgia.

APPROACH TO REGIONAL RHEUMATIC COMPLAINTS

Although all patients should be evaluated in a logical and thorough manner, many cases with focal musculoskeletal complaints are caused by commonly encountered disorders that exhibit a predictable pattern of onset, evolution, and localization; they can often be diagnosed immediately on the basis of limited historic information and selected maneuvers or tests. Although nearly every joint could be approached in this manner, the evaluation of four common involved anatomic regions—the hand, shoulder, hip, and knee—are reviewed here.

HAND PAIN

Focal or unilateral hand pain may result from trauma, overuse, infection, or a reactive or crystal-induced arthritis. By contrast, bilateral hand complaints commonly suggest a degenerative (e.g., OA), systemic, or inflammatory/immune (e.g., RA) etiology. The distribution or pattern of joint involvement is highly suggestive of certain disorders **(Fig. 18-3)**. Thus, OA (or degenerative arthritis) may manifest as distal interphalangeal (DIP) and PIP joint pain with bony hypertrophy sufficient to produce Heberden's and Bouchard's nodes, respectively. Pain, with or without bony swelling, involving the base of the thumb (first carpometacarpal joint) is also highly suggestive of OA. By contrast, RA tends to involve the PIP, MCP, intercarpal, and carpometacarpal joints (wrist) with pain, prolonged stiffness, and palpable synovial tissue hypertrophy. Psoriatic arthritis may mimic the pattern of joint involvement seen in OA (DIP and PIP joints), but can be distinguished by the presence of inflammatory signs (erythema, warmth, synovial swelling), with or without carpal involvement, nail pitting, or onycholysis. Hemochromatosis should be considered when degenerative changes (bony hypertrophy) are seen at the second and third MCP joints with associated chondrocalcinosis or episodic, inflammatory wrist arthritis.

Soft tissue swelling over the dorsum of the hand and wrist may suggest an inflammatory extensor tendon tenosynovitis possibly caused by gonococcal infection, gout, or inflammatory arthritis (e.g., RA). Tenosynovitis is suggested by localized warmth, swelling, or pitting edema and may be confirmed when the soft tissue swelling tracks with tendon movement, such as flexion and extension of fingers or when pain is induced while stretching the extensor tendon sheaths (flexing the digits distal to the MCP joints and maintaining the wrist in a fixed, neutral position).

Focal wrist pain localized to the radial aspect may be caused by de Quervain's tenosynovitis resulting from inflammation of the tendon sheath(s) involving the abductor pollicis longus or extensor pollicis brevis (Fig. 18-3). This commonly results from overuse or follows pregnancy and may be diagnosed with Finkelstein's test. A positive result is present when radial wrist pain is induced after the thumb is flexed and placed inside a clenched fist and the patient actively deviates the hand downward with ulnar deviation at the wrist. Carpal tunnel syndrome is another common disorder of the upper extremity and results from compression of the median nerve within the carpal tunnel. Manifestations include pain in the wrist that may radiate with paresthesia to the thumb, second and third fingers, and

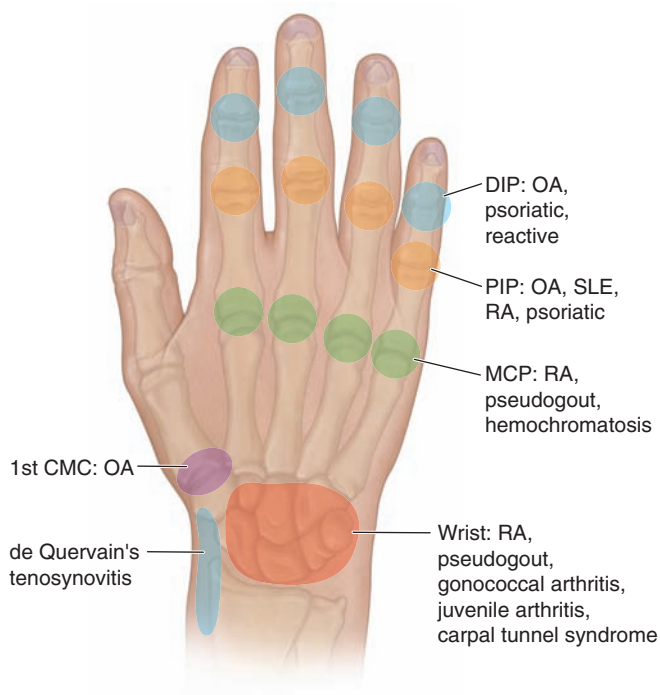


FIGURE 18-3
Sites of hand or wrist involvement and their potential disease associations. CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. (*From JJ Cush et al: Evaluation of musculoskeletal complaints, in Rheumatology: Diagnosis and Therapeutics, 2nd ed, JJ Cush et al (eds). Philadelphia, Lippincott Williams & Wilkins, 2005, pp 3-20 with permission.*)

radial half of the fourth finger and, at times, atrophy of thenar musculature. Carpal tunnel syndrome is commonly associated with pregnancy, edema, trauma, OA, inflammatory arthritis, and infiltrative disorders (e.g., amyloidosis). The diagnosis may be suggested by a positive Tinel's or Phalen's sign. With each test, paresthesia in a median nerve distribution is induced or increased by either "thumping" the volar aspect of the wrist (Tinel's sign) or pressing the extensor surfaces of both flexed wrists against each other (Phalen's sign). The variable sensitivity of these tests may require nerve conduction velocity testing to confirm a suspected diagnosis.

SHOULDER PAIN

During the evaluation of shoulder disorders, the examiner should carefully note any history of trauma, fibromyalgia, infection, inflammatory disease, occupational hazards, or previous cervical disease. In addition, the patient should be questioned as to the activities or movement(s) that elicit shoulder pain. While arthritis is suggested by pain on movement in all planes, pain with specific active motion suggests a periarticular (nonarticular) process. Shoulder pain may originate in the glenohumeral or acromioclavicular joints, subacromial (subdeltoid) bursa, periarticular soft tissues (e.g., fibromyalgia, rotator cuff tear/tendinitis), or cervical spine **(Fig. 18-4)**. Shoulder pain is referred frequently from the cervical spine but may also be referred from intrathoracic lesions (e.g., a Pancoast tumor) or from gall bladder, hepatic, or diaphragmatic disease. Fibromyalgia should be suspected when glenohumeral pain is accompanied by diffuse periarticular (i.e., subacromial, bicipital) pain and tender points (i.e., trapezius or supraspinatus). The shoulder should be put through its full range of motion both actively and passively (with examiner assistance): forward flexion, extension, abduction, adduction, and internal and external rotation. Manual inspection of the periarticular structures will often provide important diagnostic information. Glenohumeral involvement is best detected by placing the thumb over the glenohumeral joint and applying pressure anteriorly while internally and externally rotating the humeral head. The examiner should apply direct manual pressure over the subacromial bursa that lies lateral to and immediately beneath the acromion (Fig. 18-4). Subacromial bursitis is a frequent cause of shoulder pain. Anterior to the subacromial bursa, the bicipital tendon traverses the bicipital groove. This tendon is best identified by palpating it in its groove as the patient rotates the humerus internally and externally. Direct pressure over the tendon may reveal pain indicative of bicipital tendinitis. Palpation of the acromioclavicular joint may disclose local pain, bony hypertrophy, or, uncommonly, synovial swelling. Whereas OA and RA commonly affect

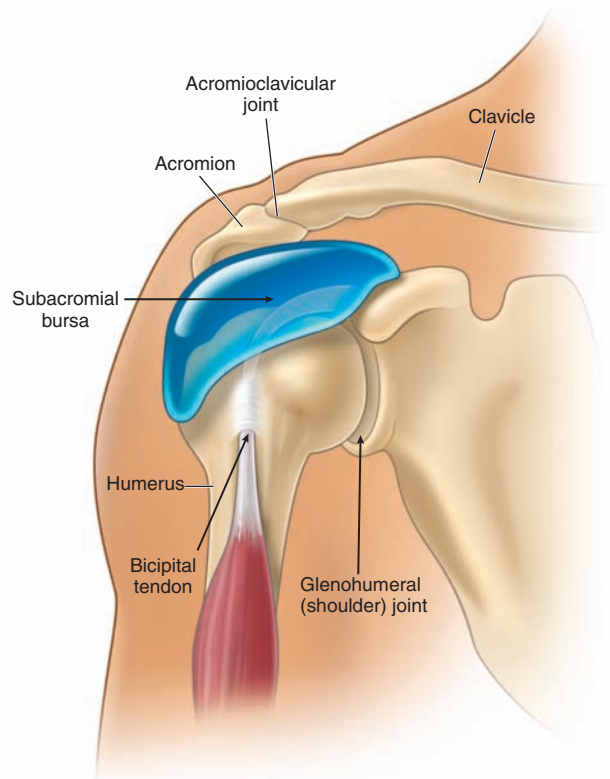


FIGURE 18-4
Origins of shoulder pain. The schematic diagram of the shoulder indicates with arrows the most common causes and locations of shoulder pain.

the acromioclavicular joint, OA seldom involves the glenohumeral joint, unless there is a traumatic or occupational cause. The glenohumeral joint is best palpated anteriorly by placing the thumb over the humeral head (just medial and inferior to the coracoid process) and having the patient rotate the humerus internally and externally. Pain localized to this region is indicative of glenohumeral pathology. Synovial effusion or tissue is seldom palpable but, if present, may suggest infection, RA, or an acute tear of the rotator cuff.

Rotator cuff tendinitis or tear is a very common cause of shoulder pain. The rotator cuff is formed by the tendons of the supraspinatus, infraspinatus, teres minor, and subscapularis muscles. Rotator cuff tendinitis is suggested by pain on active abduction (but not passive abduction), pain over the lateral deltoid muscle, night pain, and evidence of the impingement sign. This maneuver is performed by the examiner raising the patient's arm into forced flexion while stabilizing and preventing rotation of the scapula. A positive sign is present if pain develops before 180° of forward flexion. A complete tear of the rotator cuff is more common in the elderly and often results from trauma; it may manifest in the same manner as tendinitis but is less common. The diagnosis is also suggested by the drop arm test in which the patient is unable to maintain his

or her arm outstretched once it is passively abducted. If the patient is unable to hold the arm up once 90° of abduction is reached, the test is positive. Tendinitis or tear of the rotator cuff can be confirmed by magnetic resonance imaging (MRI) or ultrasound.

KNEE PAIN

Knee pain may result from intraarticular (OA, RA) or periarticular (anserine bursitis, collateral ligament strain) processes or be referred from hip pathology. A careful history should delineate the chronology of the knee complaint and whether there are predisposing conditions, trauma, or medications that might underlie the complaint. For example, patellofemoral disease (e.g., OA) may cause anterior knee pain that worsens with climbing stairs. Observation of the patient's gait is also important. The knee should be carefully inspected in the upright (weight-bearing) and prone positions for swelling, erythema, malalignment, visible trauma (contusion, laceration), or muscle wasting. The most common form of malalignment in the knee is *genu varum* (bowlegs) or *genu valgum* (knock-knees). Bony swelling of the knee joint commonly results from hypertrophic osseous changes seen with disorders such as OA and neuropathic arthropathy. Swelling caused by hypertrophy of the synovium or synovial effusion may manifest as a fluctuant, ballotable, or soft tissue enlargement in the suprapatellar pouch (suprapatellar reflection of the synovial cavity) or regions lateral and medial to the patella. Synovial effusions may also be detected by balloting the patella downward toward the femoral groove or by eliciting a "bulge sign." With the knee extended the examiner should manually compress, or "milk," synovial fluid down from the suprapatellar pouch and lateral to the patellae. The application of manual pressure lateral to the patella may cause an observable shift in synovial fluid (bulge) to the medial aspect. The examiner should note that this maneuver is only effective in detecting small to moderate effusions (<100 mL). Inflammatory disorders such as RA, gout, pseudogout, and reactive arthritis may involve the knee joint and produce significant pain, stiffness, swelling, or warmth. A popliteal or *Baker's cyst* is best palpated with the knee partially flexed and is best viewed posteriorly with the patient standing and knees fully extended to visualize isolated or unilateral popliteal swelling or fullness.

Anserine bursitis is an often missed periarticular cause of knee pain in adults. The pes anserine bursa underlies the insertion of the conjoined tendons (sartorius, gracilis, semitendinosis) on the anteromedial proximal tibia and may be painful following trauma, overuse, or inflammation. It is often tender in patients with fibromyalgia, obesity, and knee osteoarthritis. Other forms of bursitis may also present as knee pain. The prepatellar bursa is superficial and is located over the inferior portion of the patella. The infrapatellar bursa is deeper and lies beneath the patellar ligament before its insertion on the tibial tubercle.

Internal derangement of the knee may result from trauma or degenerative processes. Damage to the meniscal cartilage (medial or lateral) frequently presents as chronic or intermittent knee pain. Such an injury should be suspected when there is a history of trauma, athletic activity, or chronic knee arthritis, and when the patient relates symptoms of "locking," clicking, or "giving way" of the joint. With the knee flexed 90° and the patient's foot on the table, pain elicited during palpation over the joint line or when the knee is stressed laterally or medially may suggest a meniscal tear. A positive McMurray test may also indicate a meniscal tear. To perform this test, the knee is first flexed at 90°, and the leg is then extended while the lower extremity is simultaneously torqued medially or laterally. A painful click during inward rotation may indicate a lateral meniscus tear, and pain during outward rotation may indicate a tear in the medial meniscus. Lastly, damage to the cruciate ligaments should be suspected with acute onset of pain, possibly with swelling, a history of trauma, or a synovial fluid aspirate that is grossly bloody. Examination of the cruciate ligaments is best accomplished by eliciting a drawer sign. With the patient recumbent, the knee should be partially flexed and the foot stabilized on the examining surface. The examiner should manually attempt to displace the tibia anteriorly or posteriorly with respect to the femur. If anterior movement is detected, then anterior cruciate ligament damage is likely. Conversely, significant posterior movement may indicate posterior cruciate damage. Contralateral comparison will assist the examiner in detecting significant anterior or posterior movement.

HIP PAIN

The hip is best evaluated by observing the patient's gait and assessing range of motion. The vast majority of patients reporting "hip pain" localize their pain unilaterally to the posterior gluteal musculature **(Fig. 18-5)**. Such pain tends to radiate down the posterolateral aspect of the thigh and may or may not be associated with complaints of low back pain. This presentation frequently results from degenerative arthritis of the lumbosacral spine or disks and commonly follows a dermatomal distribution with involvement of nerve roots between L4 and S1. Sciatica is caused by impingement of the L4, L5, or S1 nerve (i.e., from a herniated disk) and manifests as unilateral neuropathic pain extending from the gluteal region down the posterolateral leg to the foot. Some individuals instead localize their "hip pain" laterally to the area overlying

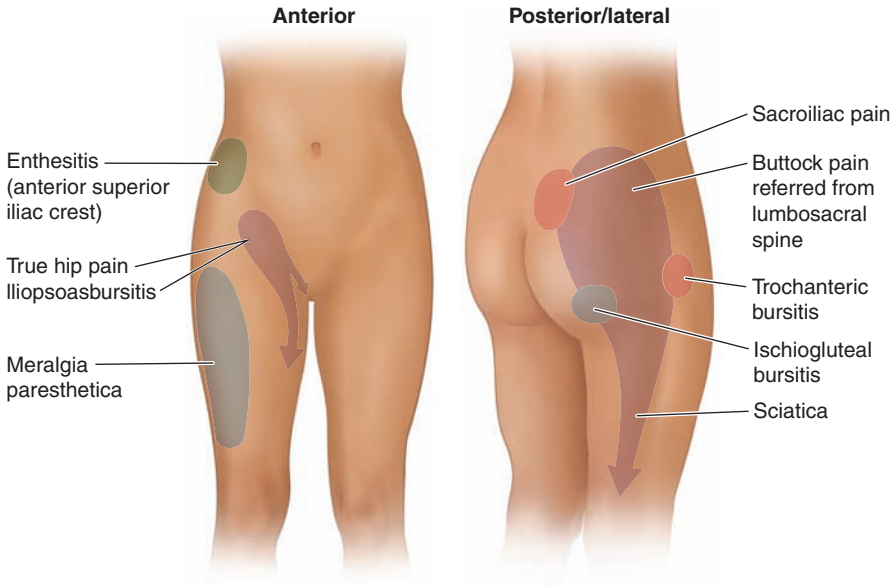


FIGURE 18-5
Origins of hip pain and dysesthesias. (*From JJ Cush et al: Evaluation of musculoskeletal complaints, in Rheumatology: Diagnosis and Therapeutics, 2nd ed, JJ Cush et al (eds). Philadelphia, Lippincott Williams & Wilkins, 2005, pp 3-20 with permission.*)

the trochanteric bursa. Because of the depth of this bursa, swelling and warmth are usually absent. Diagnosis of trochanteric bursitis can be confirmed by inducing point tenderness over the trochanteric bursa. Gluteal and trochanteric pain may also indicate underlying fibromyalgia. Range of movement may be limited by pain. Pain in the hip joint is less common and tends to be located anteriorly, over the inguinal ligament; it may radiate medially to the groin. Uncommonly, iliopsoas bursitis may mimic true hip joint pain. Diagnosis of iliopsoas bursitis may be suggested by a history of trauma or inflammatory arthritis. Pain associated with iliopsoas bursitis is localized to the groin or anterior thigh and tends to worsen with hyperextension of the hip; many patients prefer to flex and externally rotate the hip to reduce the pain from a distended bursa.

LABORATORY INVESTIGATIONS

The vast majority of musculoskeletal disorders can be easily diagnosed by a complete history and physical examination. An additional objective of the initial encounter is to determine whether additional investigations or immediate therapy is required. A number of features indicate the need for additional evaluation. Monarticular conditions require additional evaluation, as do traumatic or inflammatory conditions and conditions accompanied by neurologic changes or systemic manifestations of serious disease. Finally, individuals with chronic symptoms (>6 weeks), especially when there has been a lack of response to symptomatic measures, are candidates for additional evaluation. The extent and nature of the additional investigation should be dictated by the clinical features and suspected pathologic process. Laboratory tests should be used to confirm a specific clinical diagnosis and not be used to screen or evaluate patients with vague rheumatic complaints. Indiscriminate use of broad batteries of diagnostic tests and radiographic procedures is rarely a useful or cost-effective means to establish a diagnosis.

Besides a complete blood count, including a white blood cell (WBC) and differential count, the routine evaluation should include a determination of an acute-phase reactant such as the ESR or CRP, which can be useful in discriminating inflammatory from noninflammatory disorders. Both are inexpensive, easily obtained, and may be elevated with infection, inflammation, autoimmune disorders, neoplasia, pregnancy, renal insufficiency, advanced age, and hyperlipidemia. Extreme elevation of the acute-phase reactants (CRP, ESR) is seldom seen without evidence of serious illness (e.g., sepsis, pleuropericarditis, polymyalgia rheumatica, giant cell arteritis, adult Still's disease).

Serum uric acid determinations are useful in the diagnosis of gout and in monitoring the response to urate-lowering therapy. Uric acid, the end product of purine metabolism, is primarily excreted in the urine. Serum values range from 238 to 516 mol/L (4.0–8.6 mg/dL) in men; the lower values (178–351 mol/L [3.0–5.9 mg/dL]) seen in women are caused by the uricosuric effects of estrogen. Urinary uric acid levels are normally <750 mg per 24 h. Although hyperuricemia (especially levels >535 mol/L [9 mg/dL]) is associated with an increased incidence of gout and nephrolithiasis, levels may not correlate with the severity of articular disease. Uric acid levels (and the risk of gout) may be increased by inborn errors of metabolism (Lesch-Nyhan syndrome), disease states (renal insufficiency, myeloproliferative disease, psoriasis), or drugs (alcohol, cytotoxic

therapy, thiazides). Although nearly all patients with gout will demonstrate hyperuricemia at some time during their illness, up to 5% of patients with an acute gouty attack will have normal serum uric acid levels, presumably from acute inflammation augmented excretion of uric acid. Monitoring serum uric acid may be useful in assessing the response to hypouricemic therapy or chemotherapy as the goal of therapy is to lower serum urate below 6 mg/dL.

Serologic tests for rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibodies, antinuclear antibodies (ANA), complement levels, Lyme and antineutrophil cytoplasmic antibodies (ANCA), or antistreptolysin O (ASO) titer should be carried out only when there is clinical evidence to suggest an associated diagnosis, as these have poor predictive value when used for screening, especially when the pretest probability is low. Although 4–5% of a healthy population will have positive tests for RF and ANAs, only 1% and <0.4% of the population will have RA or SLE, respectively. IgM RF (autoantibodies against the Fc portion of IgG) is found in 80% of patients with RA and may also be seen in low titers in patients with chronic infections (tuberculosis, leprosy, hepatitis); other autoimmune diseases (SLE, Sjögren's syndrome); and chronic pulmonary, hepatic, or renal diseases. When considering RA, both serum RF and anti-CCP antibodies should be obtained as these are complementary. Both are comparably sensitive, but CCP antibodies are more specific than RF. In RA, the presence of anti-CCP and rheumatoid factor antibodies may indicate a greater risk for more severe, erosive polyarthritis. ANAs are found in nearly all patients with SLE and may also be seen in patients with other autoimmune diseases (polymyositis, scleroderma, antiphospholipid syndrome, Sjogren's syndrome), drug-induced lupus (resulting from hydralazine, procainamide, quinidine, tetracyclines, tumor necrosis factor inhibitors), chronic liver or renal disorders, and advanced age. Positive ANAs are found in 5% of adults and in up to 14% of elderly or chronically ill individuals. The ANA test is very sensitive but poorly specific for lupus, as <5% of all positive results will be caused by lupus alone. The interpretation of a positive ANA test may depend on the magnitude of the titer and the pattern observed by immunofluorescence microscopy **(Table 18-4)**. Diffuse and speckled patterns are least specific, whereas a peripheral, or rim, pattern (related to autoantibodies against double-strand [native] DNA) is highly specific and suggestive of lupus. Centromeric patterns are seen in patients with limited scleroderma (*c*alcinosis, *R*aynaud's *p*henomenon, *e*sophageal involvement, *s*clerodactyly, *t*elangiectasia [CREST] syndrome) or primary biliary sclerosis, and nucleolar patterns may be seen in patients with diffuse systemic sclerosis or inflammatory myositis.

TABLE 18-4

ANTINUCLEAR ANTIBODY (ANA) PATTERNS AND CLINICAL ASSOCIATIONS

ANA PATTERN	ANTIGEN IDENTIFIED	CLINICAL CORRELATE
Diffuse	Deoxyribonucleoprotein	Nonspecific
	Histones	Drug-induced lupus, lupus
Peripheral (rim)	ds-DNA	50% of SLE (specific)
Speckled	U1-RNP	>90% of MCTD
	Sm	30% of SLE (specific)
	Ro (SS-A)	Sjögrens 60%, SCLE, neonatal lupus, ANA(–) lupus
	La (SS-B)	50% of Sjögrens, 15% lupus
	Scl-70	40% of diffuse scleroderma
	PM-1	Polymyositis (PM), dermatomyositis
	Jo-1	PM w/pneumonitis + arthritis
Nucleolar	RNA polymerase I, others	40% of PSS
Centromere	Kinetochore	75% CREST (limited scleroderma)

Abbreviations: ANA, antinuclear antibody; CREST, *c*alcinosis, *R*aynaud phenomenon, *e*sophageal involvement; *s*clerodactyly; and *t*elangiectasia; MCTD, mixed connective tissue disease; PSS, progressive systemic sclerosis; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

Aspiration and analysis of synovial fluid are always indicated in acute monarthritis or when an infectious or crystal-induced arthropathy is suspected. Synovial fluid may distinguish between noninflammatory and inflammatory processes by analysis of the appearance, viscosity, and cell count. Tests for synovial fluid glucose, protein, lactate dehydrogenase, lactic acid, or autoantibodies are not recommended as they have no diagnostic value. Normal synovial fluid is clear or a pale straw color and is viscous, primarily because of the high levels of hyaluronate. Noninflammatory synovial fluid is clear, viscous, and amber-colored, with a white blood cell count of <2000/ L and a predominance of mononuclear cells. The viscosity of synovial fluid is assessed by expressing fluid from the syringe one drop at a time. Normally, there is a stringing effect, with a long tail behind each synovial drop. Effusions caused by OA or trauma will have normal viscosity. Inflammatory fluid is turbid and yellow, with an increased white cell count (2000–50,000/ L) and a polymorphonuclear leukocyte predominance. Inflammatory fluid has reduced viscosity, diminished hyaluronate, and little or no tail following each drop of synovial fluid. Such effusions

are found in RA, gout, and other inflammatory arthritides. Septic fluid is opaque and purulent, with a WBC count usually >50,000/ L, a predominance of polymorphonuclear leukocytes (>75%), and low viscosity. Such effusions are typical of septic arthritis, but may occur with RA or gout. In addition, hemorrhagic synovial fluid may be seen with trauma, hemarthrosis, or neuropathic arthritis. An algorithm for synovial fluid aspiration and analysis is shown in **Fig. 18-6**. Synovial fluid should be analyzed immediately for appearance, viscosity, and cell count. Monosodium urate crystals (observed in gout) are seen by polarized microscopy and are long, needle-shaped, negatively birefringent, and usually intracellular. In chondrocalcinosis and pseudogout, calcium pyrophosphate dihydrate crystals are usually short, rhomboid-shaped, and positively birefringent. Whenever infection is suspected, synovial fluid should be Gram-stained and cultured appropriately. If gonococcal arthritis is suspected, immediate plating of the fluid on appropriate culture medium is indicated. Synovial fluid from patients with chronic monarthritis should also be cultured for *M. tuberculosis* and fungi. Last, it should be noted that crystal-induced and septic arthritis occasionally occur together in the same joint.

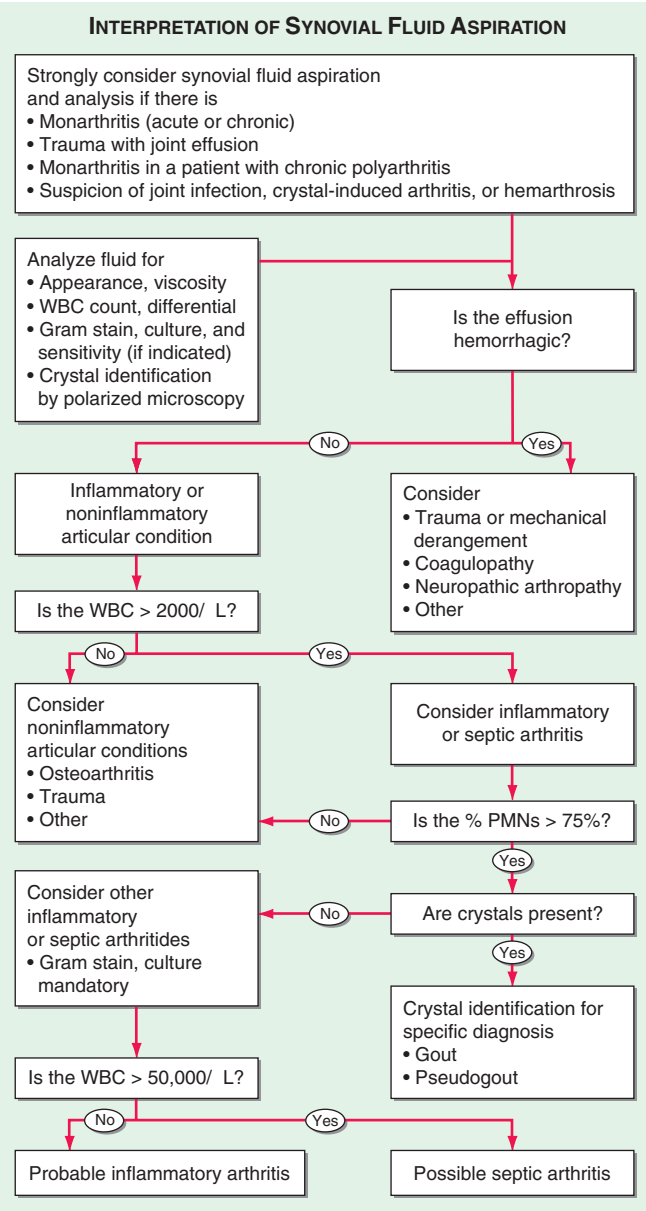


FIGURE 18-6
Algorithmic approach to the use and interpretation of synovial fluid aspiration and analysis. PMNs, polymorphonuclear (leukocytes); WBC, white blood cell (count).

DIAGNOSTIC IMAGING IN JOINT DISEASES

Conventional radiography has been a valuable tool in the diagnosis and staging of articular disorders. Plain x-rays are most appropriate when there is a history of trauma, suspected chronic infection, progressive disability, or monarticular involvement; when therapeutic alterations are considered; or when a baseline assessment is desired for what appears to be a chronic process. However, in acute inflammatory arthritis, early radiography is rarely helpful in establishing a diagnosis and may only reveal soft tissue swelling or juxtaarticular demineralization. As the disease progresses, calcification (of soft tissues, cartilage, or bone), joint space narrowing, erosions, bony ankylosis, new bone formation (sclerosis, osteophytes, or periostitis), or subchondral cysts may develop and suggest specific clinical entities. Consultation with a radiologist will help define the optimal imaging modality, technique, or positioning and prevent the need for further studies.

Additional imaging techniques may possess greater diagnostic sensitivity and facilitate early diagnosis in a limited number of articular disorders and in selected circumstances and are indicated when conventional radiography is inadequate or nondiagnostic **(Table 18-5)**. *Ultrasonography* is useful in the detection of soft tissue abnormalities, such as tenosynovitis, that cannot be fully appreciated by clinical examination. Owing to low cost, portability, and wider use, ultrasound use has grown and is the preferred method for the evaluation of synovial (Baker's) cysts, rotator cuff tears, tendinitis and tendon injury, and suspected early synovitis. Its utility is enhanced by operator experience. *Radionuclide scintigraphy* provides useful information regarding the metabolic status of bone and, along with radiography, is well suited for total-body assessment of the extent and distribution of skeletal involvement. Radionuclide imaging is a very sensitive, but poorly specific, means of detecting inflammatory or metabolic alterations in bone or periarticular soft tissue structures. The limited tissue

TABLE 18-5

DIAGNOSTIC IMAGING TECHNIQUES FOR MUSCULOSKELETAL DISORDERS

METHOD	IMAGING TIME, h	COST[a]	CURRENT INDICATIONS
Ultrasound[b]	<1	++	Synovial cysts Rotator cuff tears Tendon injury
Radionuclide scintigraphy			
^{99m}Tc	1–4	++	Metastatic bone survey Evaluation of Paget's disease Acute and chronic osteomyelitis
^{111}In-WBC	24	+++	Acute infection Prosthetic infection Acute osteomyelitis
^{67}Ga	24–48	++++	Acute and chronic infection Acute osteomyelitis
Computed tomography	<1	+++	Herniated intervertebral disk Sacroiliitis Spinal stenosis Spinal trauma Osteoid osteoma Stress fracture
Magnetic resonance imaging	1/2–2	++++	Avascular necrosis Osteomyelitis Intraarticular derangement and soft tissue injury Derangements of axial skeleton and spinal cord Herniated intervertebral disk Pigmented villonodular synovitis Inflammatory and metabolic muscle pathology

[a]Relative cost for imaging study.
[b]Results depend on operator.

contrast resolution of scintigraphy may obscure the distinction between a bony or periarticular process and may necessitate the additional use of MRI. Scintigraphy, using ^{99m}Tc, ^{67}Ga, or ^{111}In-labeled WBCs has been applied to a variety of articular disorders with variable success (Table 18-5). Although [^{99m}Tc] pertechnate or diphosphate scintigraphy **(Fig. 18-7)** may be useful in identifying osseous infection, neoplasia, inflammation, increased blood flow, bone remodeling, heterotopic bone formation, or avascular necrosis, MRI is preferred in most instances. The poor specificity of ^{99m}Tc

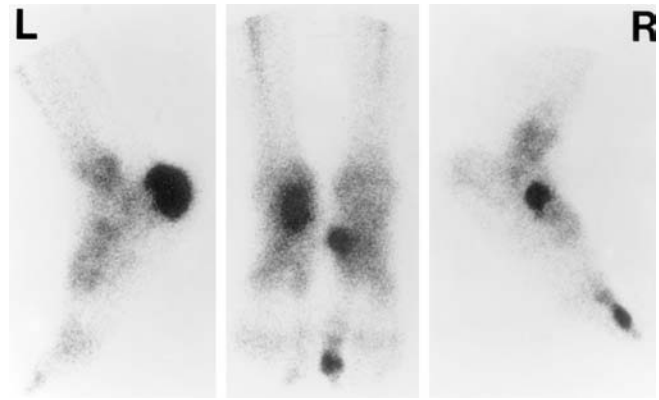


FIGURE 18-7

[^{99m}Tc]Diphosphonate scintigraphy of the feet of a 33-year-old African-American male with reactive arthritis, manifested by sacroiliitis, urethritis, uveitis, asymmetric oligoarthritis, and enthesitis. This bone scan demonstrates increased uptake indicative of enthesitis involving the insertions of the left Achilles tendon, plantar aponeurosis, and right tibialis posterior tendon as well as arthritis of the right first interphalangeal joint.

scanning has largely limited its use to surveys for bone metastases and Paget's disease of bone. Gallium scanning utilizes ^{67}Ga, which binds serum and cellular transferrin and lactoferrin, and is preferentially taken up by neutrophils, macrophages, bacteria, and tumor tissue (e.g., lymphoma). As such, it is primarily used in the identification of occult infection or malignancy. Scanning with ^{111}In-labeled WBCs has been used to detect osteomyelitis and infectious or inflammatory arthritis. Nevertheless, the use of ^{111}In-labeled WBC or ^{67}Ga scanning has largely been replaced by MRI, except when there is a suspicion of prosthetic joint infections.

CT provides detailed visualization of the axial skeleton. Articulations previously considered difficult to visualize by radiography (e.g., zygapophyseal, sacroiliac, sternoclavicular, hip joints) can be effectively evaluated using CT. CT has been demonstrated to be useful in the diagnosis of low back pain syndromes (e.g., spinal stenosis vs. herniated disk), sacroiliitis, osteoid osteoma, and stress fractures. Helical or spiral CT (with or without contrast angiography) is a novel technique that is rapid, cost-effective, and sensitive in diagnosing pulmonary embolism or obscure fractures, often in the setting of initially equivocal findings. High-resolution CT can be advocated in the evaluation of suspected or established infiltrative lung disease (e.g., scleroderma or rheumatoid lung). The recent use of hybrid (positron emission tomography [PET]/CT or single-photon emission CT [SPECT]) scans in metastatic evaluations have incorporated CT to provide better anatomic localization of scintigraphic abnormalities.



FIGURE 18-8

Superior sensitivity of MRI in the diagnosis of osteonecrosis of the femoral head. A 45-year-old woman receiving highdose glucocorticoids developed right hip pain. Conventional x-rays (*top*) demonstrated only mild sclerosis of the right femoral head. T1-weighted MRI (*bottom*) demonstrated low-density signal in the right femoral head, diagnostic of osteonecrosis.

MRI has significantly advanced the ability to image musculoskeletal structures. MRI has the advantages of providing multiplanar images with fine anatomic detail and contrast resolution **(Fig. 18-8)** that allows for the superior ability to visualize bone marrow and soft tissue periarticular structures. Although more costly with a longer procedural time than CT, the MRI has become the preferred technique when evaluating complex musculoskeletal disorders.

MRI can image fascia, vessels, nerve, muscle, cartilage, ligaments, tendons, pannus, synovial effusions, and bone marrow. Visualization of particular structures can be enhanced by altering the pulse sequence to produce either T1- or T2-weighted spin echo, gradient echo, or inversion recovery (including short tau inversion recovery [STIR]) images. Because of its sensitivity to changes in marrow fat, MRI is a sensitive but nonspecific means of detecting osteonecrosis, osteomyelitis, and marrow inflammation indicating overlying synovitis or osteitis (Fig. 18-8). Because of its enhanced soft tissue resolution, MRI is more sensitive than arthrography or CT in the diagnosis of soft tissue injuries (e.g., meniscal and rotator cuff tears); intraarticular derangements; marrow abnormalities (osteonecrosis, myeloma); and spinal cord or nerve root damage or synovitis.

CHAPTER 19

OSTEOARTHRITIS

David T. Felson

Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and the high rate of disability related to disease make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, is increasing in prevalence, the occurrence of osteoarthritis is on the rise. In the United States, osteoarthritis prevalence will increase by 66–100% by 2020.

OA affects certain joints, yet spares others (Fig. 19-1). Commonly affected joints include the cervical and lumbosacral spine, hip, knee, and first metatarsal phalangeal joint (MTP). In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. Our joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips) Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses.

OA can be diagnosed based on structural abnormalities or on the symptoms these abnormalities evoke. According to cadaveric studies, by elderly years, structural changes of OA are nearly universal. These include cartilage loss (seen as joint space loss on x-rays) and osteophytes. Many persons with x-ray evidence of OA have no joint symptoms and, while the prevalence of structural abnormalities is of interest in understanding disease pathogenesis, what matters more from a clinical perspective is the prevalence of symptomatic OA. Symptoms, usually joint pain, determine disability, visits to clinicians, and disease costs.

Symptomatic OA of the knee (pain on most days of a recent month in a knee plus x-ray evidence of OA in that knee) occurs in ~12% of persons age ≤60 in the United States and 6% of all adults age ≤30. Symptomatic hip OA is roughly one-third as common as disease in the knee. While radiographically evident hand OA and the appearance of bony enlargement in affected hand joints (Fig. 19-2) are extremely common in older persons, most cases are often not symptomatic. Even so, symptomatic hand OA occurs in ~10% of elderly individuals and often produces measurable limitation in function.

The prevalence of OA rises strikingly with age. Regardless of how it is defined, OA is uncommon in adults under age 40 and highly prevalent in those over age 60. It is also a disease that, at least in middle-aged and elderly persons, is much more common in women than in men, and sex differences in prevalence increase with age.

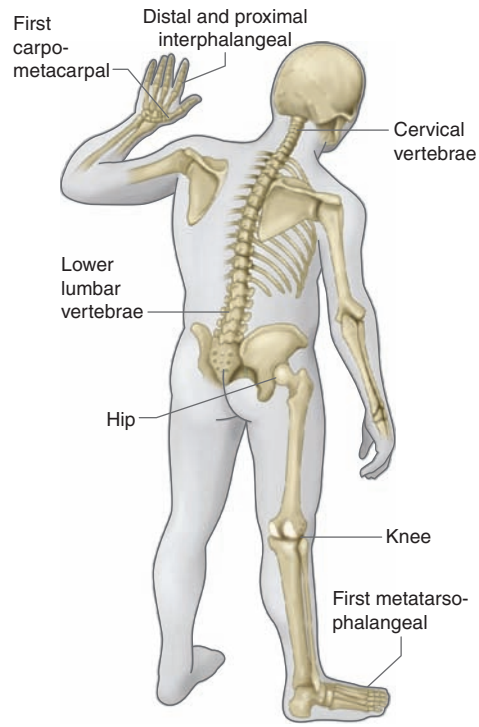


FIGURE 19-1
Joints affected by osteoarthritis.



FIGURE 19-2
Severe osteoarthritis of the hands affecting the distal interphalangeal joints (Heberden's nodes) and the proximal interphalangeal joints (Bouchard's nodes). There is no clear bony enlargement of the other common site in the hands, the thumb base.

X-ray evidence of OA is common in the lower back and neck, but back pain and neck pain have not been tied to findings of OA on x-ray. Thus, back pain and neck pain are treated separately.

DEFINITION

OA is joint failure, a disease in which all structures of the joint have undergone pathologic change, often in concert. The pathologic sine qua non of disease is hyaline articular cartilage loss, present in a focal and, initially, nonuniform manner. This is accompanied by increasing thickness and sclerosis of the subchondral bony plate, by outgrowth of osteophytes at the joint margin, by stretching of the articular capsule, by mild synovitis in many affected joints, and by weakness of muscles bridging the joint. In knees, meniscal degeneration is part of the disease. There are numerous pathways that lead to joint failure, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

JOINT PROTECTIVE MECHANISMS AND THEIR FAILURE

Joint protectors include: joint capsule and ligaments, muscle, sensory afferents, and underlying bone. Joint capsule and ligaments serve as joint protectors by providing a limit to excursion, thereby fixing the range of joint motion.

Synovial fluid reduces friction between articulating cartilage surfaces, thereby serving as a major protector against friction-induced cartilage wear. This lubrication function depends on the molecule *lubricin*, a mucinous glycoprotein secreted by synovial fibroblasts whose concentration diminishes after joint injury and in the face of synovial inflammation.

The ligaments, along with overlying skin and tendons, contain mechanoreceptor sensory afferent nerves. These mechanoreceptors fire at different frequencies throughout a joint's range of motion, providing feedback by way of the spinal cord to muscles and tendons. As a consequence, these muscles and tendons can assume the right tension at appropriate points in joint excursion to act as optimal joint protectors, anticipating joint loading.

Muscles and tendons that bridge the joint are key joint protectors. Their contractions at the appropriate time in joint movement provide the appropriate power and acceleration for the limb to accomplish its tasks. Focal stress across the joint is minimized by muscle contraction that decelerates the joint before impact and assures that when joint impact arrives, it is distributed broadly across the joint surface.

Failure of these joint protectors increases the risk of joint injury and OA. For example, in animals, OA develops rapidly when a sensory nerve to the joint is sectioned and joint injury induced. Similarly, in humans, Charcot arthropathy, a severe and rapidly progressive OA, develops when minor joint injury occurs in the presence of posterior column peripheral neuropathy. Another example of joint protector failure is rupture of ligaments, a well-known cause of the early development of OA.

CARTILAGE AND ITS ROLE IN JOINT FAILURE

In addition to being a primary target tissue for disease, cartilage also functions as a joint protector. A thin rim of tissue at the ends of two opposing bones, cartilage is lubricated by synovial fluid to provide an almost frictionless surface across which these two bones move. The compressible stiffness of cartilage compared to bone provides the joint with impact-absorbing capacity.

Since the earliest changes of OA may occur in cartilage and abnormalities there can accelerate disease development, understanding the structure and physiology of cartilage is critical to an appreciation of disease pathogenesis. The two major macromolecules in cartilage are type 2 collagen, which provides cartilage its tensile strength, and aggrecan, a proteoglycan macromolecule linked with hyaluronic acid, which consists of highly negatively charged glycosaminoglycans. In normal cartilage, type 2 collagen is woven tightly, constraining the aggrecan molecules in the interstices between collagen strands, forcing these highly negatively charged

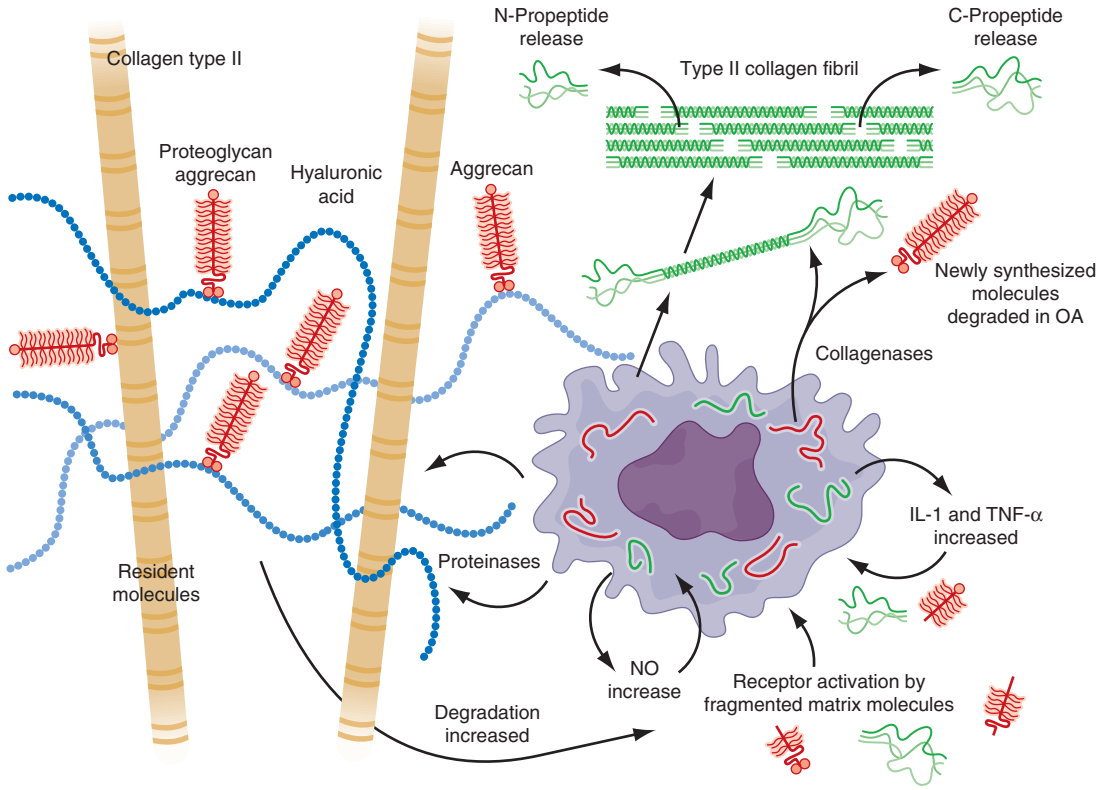


FIGURE 19-3

The chondrocyte and its products, type II collagen, aggrecan, and enzymes, which degrade these structures along with molecules stimulating chondrocytes. IL, interleukin; NO, nitric oxide; OA, osteoarthritis; TNF, tumor necrosis factor. (*From AR Poole et al: Ann Rheum Dis 61[S]:ii78, 2002.*)

molecules into close proximity with one another. The aggrecan molecule, through electrostatic repulsion of its negative charges, gives cartilage its compressive stiffness. Chondrocytes, the cells within this avascular tissue, synthesize all elements of the matrix. In addition, they produce enzymes that break down the matrix and cytokines and growth factors, which in turn provide autocrine/paracrine feedback that modulates synthesis of matrix molecules **(Fig. 19-3)**. Cartilage matrix synthesis and catabolism are in a dynamic equilibrium influenced by the cytokine and growth factor environment. Mechanical and osmotic stress on chondrocytes induces these cells to alter gene expression and increase production of inflammatory cytokines and matrix-degrading enzymes. While chondrocytes synthesize numerous enzymes, especially matrix metalloproteinases (MMP), only a few of these enzymes are critical in regulating cartilage breakdown. Type 2 cartilage is degraded primarily by MMP-13 (collagenase 3), with other collagenases playing a minor role. Aggrecan degradation is a consequence, in part, of activation of two aggrecanases (ADAMTS-4 and ADAMTS-5) and perhaps of MMPs. Both collagenase and aggrecanases act primarily in the territorial matrix surrounding chondrocytes; however, as the osteoarthritic process develops, their activities and effects spread throughout the matrix, especially in the superficial layers of cartilage.

The synovium and chondrocytes synthesize numerous growth factors and cytokines. Chief among them is interleukin (IL) 1, which exerts transcriptional effects on chondrocytes, stimulating production of proteinases and suppressing cartilage matrix synthesis. In animal models of OA, IL-1 blockade prevents cartilage loss. Tumor necrosis factor (TNF) α may play a similar role to that of IL-1. These cytokines also induce chondrocytes to synthesize prostaglandin E_2, nitric oxide, and bone morphogenic protein 2 (BMP-2), which together have complex effects on matrix synthesis and degradation. Nitric oxide inhibits aggrecan synthesis and enhances proteinase activity, whereas BMP-2 stimulates anabolic activity. At early stages in the matrix response to injury and in the healthy response to loading, the net effect of cytokine stimulation may be matrix synthesis but, ultimately, excess IL-1 triggers matrix degradation. Enzymes in the matrix are held in check by activation inhibitors, including tissue inhibitor of metalloproteinase (TIMP). Growth factors are also part of this complex network, with insulin-like growth factor type 1 and transforming growth factor

β playing prominent roles in stimulating anabolism by chondrocytes.

Whereas healthy cartilage is metabolically sluggish, with slow matrix turnover and synthesis and degradation in balance, cartilage in early OA or after an injury is highly metabolically active. In the latter situation, stimulated chondrocytes synthesize enzymes and new matrix molecules, with those enzymes becoming activated in the matrix, causing release of degraded aggrecan and type 2 collagen into cartilage and into the synovial fluid. OA cartilage is characterized by gradual depletion of aggrecan, an unfurling of the tightly woven collagen matrix, and loss of type 2 collagen. With these changes comes increasing vulnerability of cartilage, which loses its compressive stiffness.

RISK FACTORS

Joint vulnerability and joint loading are the two major factors contributing to the development of OA. On the one hand, a vulnerable joint whose protectors are dysfunctional can develop OA with minimal levels of loading, perhaps even levels encountered during everyday activities. On the other hand, in a young joint with competent protectors, a major acute injury or long-term overloading is necessary to precipitate disease. Risk factors for OA can be understood in terms of their effect either on joint vulnerability or on loading (Fig. 19-4).

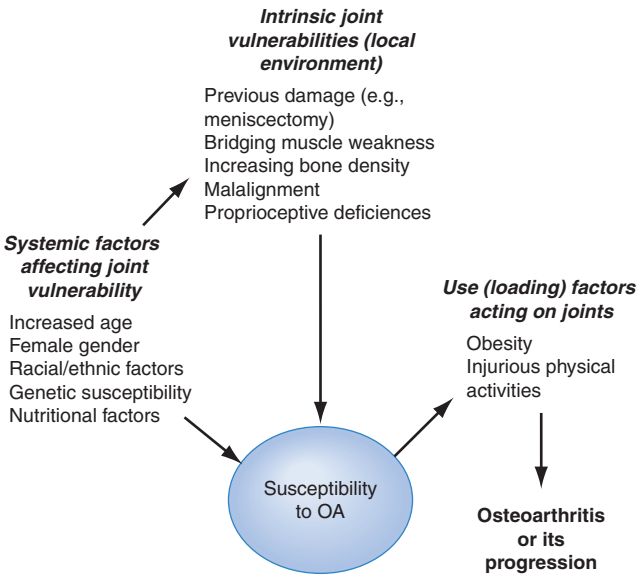


FIGURE 19-4

Risk factors for osteoarthritis either contribute to the susceptibility of the joint (systemic factors or factors in the local joint environment) or increase risk by the load they put on the joint. Usually a combination of loading and susceptibility factors is required to cause disease or its progression.

SYSTEMIC RISK FACTORS

Age is the most potent risk factor for OA. Radiographic evidence of OA is rare in individuals under age 40; however, in some joints, such as the hands, OA occurs in >50% of persons over age 70. Aging increases joint vulnerability through several mechanisms. Whereas dynamic loading of joints stimulates cartilage matrix synthesis by chondrocytes in young cartilage, aged cartilage is less responsive to these stimuli. Indeed, because of the poor responsiveness of older cartilage to such stimulation, cartilage transplant operations are far more challenging in older than in younger persons. Partly because of this failure to synthesize matrix with loading, cartilage thins with age, and thinner cartilage experiences higher shear stress at basal layers and is at greater risk of cartilage damage. Also, joint protectors fail more often with age. Muscles that bridge the joint become weaker with age and also respond less quickly to oncoming impulses. Sensory nerve input slows with age, retarding the feedback loop of mechanoreceptors to muscles and tendons related to their tension and position. Ligaments stretch with age, making them less able to absorb impulses. These factors work in concert to increase the vulnerability of older joints to OA.

Older women are at high risk of OA in all joints, a risk that emerges as women reach their sixth decade. While hormone loss with menopause may contribute to this risk, there is little understanding of the unique vulnerability of older women vs. men to OA.

HERITABILITY AND GENETICS

OA is a highly heritable disease, but its heritability varies by joint. Fifty percent of the hand and hip OA in the community is attributable to inheritance, i.e., to disease present in other members of the family. However, the heritable proportion of knee OA is at most 30%, with some studies suggesting no heritability at all. Whereas many people with OA have disease in multiple joints, this "generalized OA" phenotype is rarely inherited and is more often a consequence of aging.

Emerging evidence has identified genetic mutations that confer a high risk of OA, one of which is a polymorphism within the growth differentiation factor 5 gene. This polymorphism diminishes the quantity of GDF5, which normally has anabolic effects on the synthesis of cartilage matrix.

GLOBAL CONSIDERATIONS



Hip OA is rare in China and in immigrants from China to the United States. However, OA in the knees is at least as common, if not more so,

in Chinese than in whites from the United States, and knee OA represents a major cause of disability in China, especially in rural areas. Anatomic differences between Chinese and white hips may account for much of the difference in hip OA prevalence, with white hips having a higher prevalence of anatomic predispositions to the development of OA. Persons from Africa, but not African Americans, may also have a very low rate of hip OA.

RISK FACTORS IN THE JOINT ENVIRONMENT

Some risk factors increase vulnerability of the joint through local effects on the joint environment. With changes in joint anatomy, for example, load across the joint is no longer distributed evenly across the joint surface, but rather shows an increase in focal stress. In the hip, three uncommon developmental abnormalities occurring in utero or childhood, congenital dysplasia, Legg-Perthes disease, and slipped capital femoral epiphysis, leave a child with distortions of hip joint anatomy that often lead to OA later in life. Girls are predominantly affected by acetabular dysplasia, a mild form of congenital dislocation, whereas the other abnormalities more often affect boys. Depending on the severity of the anatomic abnormalities, hip OA occurs either in young adulthood (severe abnormalities) or middle age (mild abnormalities).

Major injuries to a joint also can produce anatomic abnormalities that leave the joint susceptible to OA. For example, a fracture through the joint surface often causes OA in joints in which the disease is otherwise rare such as the ankle and the wrist. Avascular necrosis can lead to collapse of dead bone at the articular surface, producing anatomic irregularities and subsequent OA.

Tears of ligamentous and fibrocartilaginous structures that protect the joints, such as the anterior cruciate ligament and the meniscus in the knee and the labrum in the hip, increase joint susceptibility and can lead to premature OA. Meniscal tears increase with age and when chronic are often asymptomatic but lead to adjacent cartilage damage and accelerated osteoarthritis. Even injuries that do not produce diagnosed joint injuries may increase risk of OA, perhaps because the structural injury was not detected at the time. For example, in the Framingham study subjects, men with a history of major knee injury, but no surgery, had a 3.5-fold increased risk for subsequent knee OA.

Another source of anatomic abnormality is malalignment across the joint **(Fig. 19-5)**. This factor has been best studied in the knee, which is the fulcrum of the longest lever arm in the body. Varus (bowlegged) knees with OA are at exceedingly high risk of cartilage loss in the medial or inner compartment of the knee, whereas valgus (knock-kneed) malalignment predisposes to rapid cartilage loss in the lateral compartment. Malalignment causes

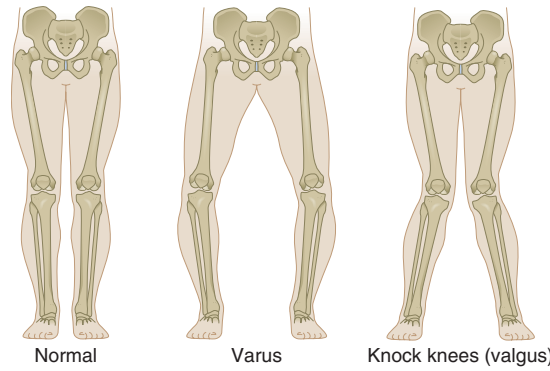


FIGURE 19-5
The two types of limb malalignment in the frontal plane: varus, in which the stress is placed across the medial compartment of the knee joint, and valgus, which places excess stress across the lateral compartment of the knee.

this effect by decreasing contact area during loading, increasing stress on a focal area of cartilage, which then breaks down. There is evidence that malalignment in the knee not only causes cartilage loss but leads to underlying bone damage, producing bone marrow lesions seen on MRI. Malalignment in the knee often produces such a substantial increase in focal stress within the knee (as evidenced by its destructive effects on subchondral bone) that severely malaligned knees may be destined to progress regardless of the status of other risk factors.

Weakness in the quadriceps muscles bridging the knee increases the risk of the development of painful OA in the knee.

Patients with knee OA have impaired proprioception across their knees, and this may predispose them to further disease progression. The role of bone in serving as a shock absorber for impact load is not well understood, but persons with increased bone density are at high risk of OA, suggesting that the resistance of bone to impact during joint use may play a role in disease development.

LOADING FACTORS

Obesity

Three to six times body weight is transmitted across the knee during single-leg stance. Any increase in weight may be multiplied by this factor to reveal the excess force across the knee in overweight persons during walking. Obesity is a well-recognized and potent risk factor for the development of knee OA and, less so, for hip OA. Obesity precedes the development of disease and is not just a consequence of the inactivity present in those with disease. It is a stronger risk factor for disease in women than in men, and in women, the relationship of weight to the risk of disease is linear, so that with each increase in weight, there is a commensurate increase in risk. Weight loss in women lowers the risk

of developing symptomatic disease. Not only is obesity a risk factor for OA in weight-bearing joints, but obese persons have more severe symptoms from the disease.

Obesity's effect on the development and progression of disease is mediated mostly through the increased loading in weight-bearing joints that occurs in overweight persons. However, a modest association of obesity with an increased risk of hand OA suggests that there may be a systemic metabolic factor circulating in obese persons that affects disease risk also.

Repeated use of joint

There are two categories of repetitive joint use, occupational use and leisure time physical activities. Workers performing repetitive tasks as part of their occupations for many years are at high risk of developing OA in the joints they use repeatedly. For example, farmers are at high risk for hip OA, and miners have high rates of OA in knees and spine, Even within a textile mill, women whose jobs required fine pincer grip (increasing the stress across the interphalangeal [IP] joints) had much more distal IP (DIP) joint OA than women whose jobs required repeated power grip, a motion that does not stress the DIP joints. Workers whose jobs require regular knee bending or lifting or carrying heavy loads have a high rate of knee OA. One reason why workers may get disease is that during long days at work, their muscles may gradually become exhausted, no longer serving as effective joint protectors.

While exercise is a major element of the treatment of OA, certain types of exercise may paradoxically increase the risk of disease. While recreational runners are not at increased risk of knee OA, studies suggest that they have a modest increased risk of disease in the hip. However, persons who have already sustained major knee injuries are at increased risk of progressive knee OA as a consequence of running. Compared to nonrunners, elite runners (professional runners and those on Olympic teams) have high risks of both knee and hip OA. Given the widespread recommendation to adopt a healthier, more exercise-filled lifestyle; longitudinal epidemiologic studies of exercise contain cautionary notes. For example, women with increased levels of physical activity, either as teenagers or at age 50, had a higher risk of developing symptomatic hip disease later in life than women who were sedentary. Other athletic activities that pose high risks of joint injury, such as football, may thereby predispose to OA.

PATHOLOGY

The pathology of OA provides evidence of the involvement of many joint structures in disease. Cartilage initially shows surface fibrillation and irregularity. As

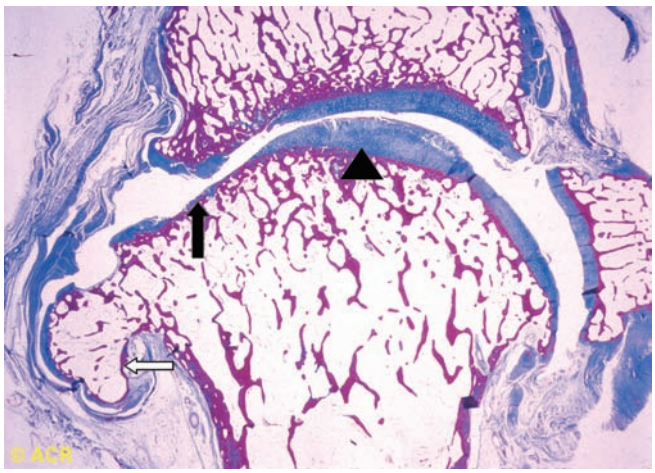


FIGURE 19-6

Pathologic changes of osteoarthritis in a toe joint. Note the nonuniform loss of cartilage (*arrowhead* vs. *solid arrow*), the increased thickness of the subchondral bone envelope (*solid arrow*), and the osteophyte (*open arrow*). (*From the American College of Rheumatology slide collection.*)

disease progresses, focal erosions develop there, and these eventually extend down to the subjacent bone. With further progression, cartilage erosion down to bone expands to involve a larger proportion of the joint surface, even though OA remains a focal disease with nonuniform loss of cartilage **(Fig. 19-6)**.

After an injury to cartilage, chondrocytes undergo mitosis and clustering. While the metabolic activity of these chondrocyte clusters is high, the net effect of this activity is to promote proteoglycan depletion in the matrix surrounding the chondrocytes. This is because the catabolic is greater than the synthetic activity. As disease develops, collagen matrix becomes damaged, the negative charges of proteoglycans get exposed, and cartilage swells from ionic attraction to water molecules. Because in damaged cartilage proteoglycans are no longer forced into close proximity, cartilage does not bounce back after loading as it did when healthy, and cartilage becomes vulnerable to further injury. Chondrocytes at the basal level of cartilage undergo apoptosis.

With loss of cartilage come alterations in subchondral bone. Stimulated by growth factors and cytokines, osteoclasts and osteoblasts in the subchondral bony plate, just underneath cartilage, become activated. Bone formation produces a thickening and stiffness of the subchondral plate that occurs even before cartilage ulcerates. Trauma to bone during joint loading may be the primary factor driving this bone response, with healing from injury (including microcracks) producing stiffness. Small areas of osteonecrosis usually exist in joints with advanced disease. Bone death may also be caused by bone trauma with shearing of microvasculature, leading to a cutoff of vascular supply to some bone areas.

At the margin of the joint, near areas of cartilage loss, osteophytes form. These start as outgrowths of new cartilage and, with neurovascular invasion from the bone, this cartilage ossifies. Osteophytes are an important radiographic hallmark of OA. In malaligned joints, osteophytes grow larger on the side of the joint subject to most loading stress (e.g., in varus knees, osteophytes grow larger on the medial side).

The synovium produces lubricating fluids that minimize shear stress during motion. In healthy joints, the synovium consists of a single discontinuous layer filled with fat and containing two types of cells, macrophages and fibroblasts, but in OA, it can sometimes become edematous and inflamed. There is a migration of macrophages from the periphery into the tissue, and cells lining the synovium proliferate. Enzymes secreted by the synovium digest cartilage matrix that has been sheared from the surface of the cartilage.

Additional pathologic changes occur in the capsule, which stretches, becomes edematous, and can become fibrotic.

The pathology of OA is not identical across joints. In hand joints with severe OA, for example, there are often cartilage erosions in the center of the joint probably produced by bony pressure from the opposite side of the joint. In hand OA, pathology has also been noted in ligament site insertions, which may help propagate disease.

Basic calcium phosphate and calcium pyrophosphate dihydrate crystals are present microscopically in most joints with end-stage OA. Their role in osteoarthritic cartilage is unclear, but their release from cartilage into the joint space and joint fluid likely triggers synovial inflammation, which can, in turn, produce release of enzymes and trigger nociceptive stimulation.

SOURCES OF PAIN

Because cartilage is aneural, cartilage loss in a joint is not accompanied by pain. Thus, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by the x-ray, and the severity of x-ray changes in OA correlates poorly with pain severity.

Based on MRI studies in osteoarthritic knees comparing those with and without pain and on studies mapping tenderness in unanesthetized joints, likely sources of pain include synovial inflammation, joint effusions, and bone marrow edema. Modest synovitis develops in many but not all osteoarthritic joints. Some diseased joints have no synovitis, whereas others have synovial inflammation that approaches the severity of joints with rheumatoid arthritis (Chap. 6). The presence of synovitis on MRI is correlated with the presence and severity of knee pain. Capsular stretching from fluid in the joint stimulates nociceptive fibers there, inducing pain. Increased focal loading as part of the disease not only damages cartilage but probably also injures the underlying bone. As a consequence, bone marrow edema appears on the MRI; histologically, this edema signals the presence of microcracks and scar, which are the consequences of trauma. These lesions may stimulate bone nociceptive fibers. Also, hemostatic pressure within bone rises in OA, and the increased pressure itself may stimulate nociceptive fibers, causing pain. Lastly, osteophytes themselves may be a source of pain. When osteophytes grow, neurovascular innervation penetrates through the base of the bone into the cartilage and into the developing osteophyte.

Pain may arise from outside the joint also, including bursae near the joints. Common sources of pain near the knee are anserine bursitis and iliotibial band syndrome.

CLINICAL FEATURES

Joint pain from OA is activity-related. Pain comes on either during or just after joint use and then gradually resolves. Examples include knee or hip pain with going up or down stairs, pain in weight-bearing joints when walking, and, for hand OA, pain when cooking. Early in disease, pain is episodic, triggered often by a day or two of overactive use of a diseased joint, such as a person with knee OA taking a long run and noticing a few days of pain thereafter. As disease progresses, the pain becomes continuous and even begins to be bothersome at night. Stiffness of the affected joint may be prominent, but morning stiffness is usually brief (<30 min).

In knees, buckling may occur, in part, due to weakness of muscles crossing the joint. Mechanical symptoms, such as buckling, catching, or locking, could also signify internal derangement, such as meniscal tears, and need to be evaluated. In the knee, pain with activities requiring knee flexion, such as stair climbing and arising from a chair, often emanates from the patellofemoral compartment of the knee, which does not actively articulate until the knee is bent ~35°.

OA is the most common cause of chronic knee pain in persons over age 45, but the differential diagnosis is long. Inflammatory arthritis is likely if there is prominent morning stiffness and many other joints are affected. Bursitis occurs commonly around knees and hips. A physical examination should focus on whether tenderness is over the joint line (at the junction of the two bones around which the joint is articulating) or is

outside of it. Anserine bursitis, medial and distal to the knee, is an extremely common cause of chronic knee pain that may respond to a glucocorticoid injection. Prominent nocturnal pain in the absence of end-stage OA merits a distinct workup. For hip pain, OA can be detected by loss of internal rotation on passive movement, and pain isolated to an area lateral to the hip joint usually reflects the presence of trochanteric bursitis.

No blood tests are routinely indicated for workup of patients with OA unless symptoms and signs suggest inflammatory arthritis. Examination of the synovial fluid is often more helpful diagnostically than an x-ray. If the synovial fluid white count is >1000 per μL, inflammatory arthritis or gout or pseudogout are likely, the latter two being also identified by the presence of crystals.

X-rays are indicated to evaluate chronic hand pain and hip pain thought to be due to OA, as the diagnosis is often unclear without confirming radiographs. For knee pain, x-rays should be obtained if symptoms or signs are not typical of OA or if knee pain persists after inauguration of effective treatment. In OA, radiographic findings **(Fig. 19-7)** correlate poorly with the presence and severity of pain. Further, radiographs may be normal in early disease as they are insensitive to cartilage loss and other early findings.

While MRI may reveal the extent of pathology in an osteoarthritic joint, it is not indicated as part of the diagnostic workup. Findings such as meniscal tears in cartilage and bone lesions occur in most patients with OA in the knee, but almost never warrant a change in therapy.

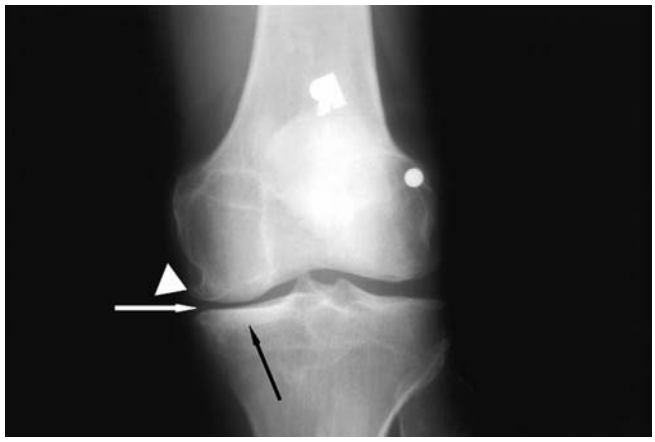


FIGURE 19-7

X-ray of knee with medial osteoarthritis. Note the narrowed joint space on medial side of the joint only (*white arrow*), the sclerosis of the bone in the medial compartment providing evidence of cortical thickening (*black arrow*), and the osteophytes in the medial femur (*white wedge*).

TREATMENT Osteoarthritis

The goals of the treatment of OA are to alleviate pain and minimize loss of physical function. To the extent that pain and loss of function are consequences of inflammation, of weakness across the joint, and of laxity and instability, the treatment of OA involves addressing each of these impairments. Comprehensive therapy consists of a multimodality approach including nonpharmacologic and pharmacologic elements.

Patients with mild and intermittent symptoms may need only reassurance or nonpharmacologic treatments. Patients with ongoing, disabling pain are likely to need both nonpharmaco- and pharmacotherapy.

Treatments for knee OA have been more completely evaluated than those for hip and hand OA or for disease in other joints. Thus, while the principles of treatment are identical for OA in all joints, we shall focus next on the treatment of knee OA, noting specific recommendations for disease in other joints, especially when they differ from those for disease in the knee.

NONPHARMACOTHERAPY Since OA is a mechanically driven disease, the mainstay of treatment involves altering loading across the painful joint and improving the function of joint protectors, so they can better distribute load across the joint. Ways of lessening focal load across the joint include

(1) avoiding activities that overload the joint, as evidenced by their causing pain;
(2) improving the strength and conditioning of muscles that bridge the joint, so as to optimize their function; and
(3) unloading the joint, either by redistributing load within the joint with a brace or a splint or by unloading the joint during weight bearing with a cane or a crutch.

The simplest effective treatment for many patients is to avoid activities that precipitate pain. For example, for the middle-aged patient whose long-distance running brings on symptoms of knee OA, a less demanding form of weight-bearing activity may alleviate all symptoms. For an older person whose daily constitutionals up and down hills bring on knee pain, routing the constitutional away from hills might eliminate symptoms.

Each pound of weight increases the loading across the knee three- to sixfold. Weight loss may have a commensurate multiplier effect, unloading both knees and hips. Thus, weight loss, especially if substantial, may lessen symptoms of knee and hip OA.

In hand joints affected by OA, splinting, by limiting motion, often minimizes pain for patients with involvement either in the base of the thumb or in the DIP or

proximal IP joints. With an appropriate splint, function can often be preserved. Weight-bearing joints such as knees and hips can be unloaded by using a cane in the hand opposite to the affected joint for partial weight bearing. A physical therapist can help teach the patient how to use the cane optimally, including ensuring that its height is optimal for unloading. Crutches or walkers can serve a similar beneficial function.

Exercise Osteoarthritic pain in knees or hips during weight bearing results in lack of activity and poor mobility and, because OA is so common, the inactivity that results represents a public health concern, increasing the risk of cardiovascular disease and of obesity. Aerobic capacity is poor in most elders with symptomatic knee OA, worse than others of the same age.

The development of weakness in muscles that bridge osteoarthritic joints is multifactorial in etiology. First, there is a decline in strength with age. Second, with limited mobility comes disuse muscle atrophy. Third, patients with painful knee or hip OA alter their gait so as to lessen loading across the affected joint, and this further diminishes muscle use. Fourth, "arthrogenous inhibition" may occur, whereby contraction of muscles bridging the joint is inhibited by a nerve afferent feedback loop emanating in a swollen and stretched joint capsule; this prevents maximal attainment of voluntary maximal strength. Since adequate muscle strength and conditioning are critical to joint protection, weakness in a muscle that bridges a diseased joint makes the joint more susceptible to further damage and pain. The degree of weakness correlates strongly with the severity of joint pain and the degree of physical limitation. One of the cardinal elements of the treatment of OA is to improve the functioning of muscles surrounding the joint.

For knee and hip OA, trials have shown that exercise lessens pain and improves physical function. Most effective exercise regimens consist of aerobic and/or resistance training, the latter of which focuses on strengthening muscles across the joint. Exercises are likely to be effective, especially if they train muscles for the activities a person performs daily. Some exercises may actually increase pain in the joint; these should be avoided, and the regimen needs to be individualized to optimize effectiveness and minimize discomfort. Range-of-motion exercises, which do not strengthen muscles, and isometric exercises that strengthen muscles, but not through range of motion, are unlikely to be effective by themselves. Isokinetic and isotonic strengthening (strengthening that occurs when a person flexes or extends the knees against resistance) have been shown consistently to be efficacious. Low-impact exercises, including water aerobics and water resistance training, are often better tolerated by patients than exercises involving impact loading, such as running or treadmill exercises. A patient should be referred to an exercise class or to a therapist who can create an individualized regimen, and then an individualized home-based regimen can be crafted.

There is no strong evidence that patients with hand OA benefit from therapeutic exercise, although for any patient with OA, individualized exercise programs should be tried. Adherence to exercise over the long term is the major challenge to an exercise prescription. In trials involving patients with knee OA, who are interested in exercise treatment, a third to over a half of patients stopped exercising by 6 months. Less than 50% continued regular exercise at 1 year. The strongest predictor of continued exercise in a patient is a previous personal history of successful exercise. Physicians should reinforce the exercise prescription at each clinic visit, help the patient recognize barriers to ongoing exercise, and identify convenient times for exercise to be done routinely. The combination of exercise with calorie restriction is especially effective in lessening pain.

One clinical trial has suggested that, among those with very early OA, participating in a strengthening and multimodality exercise program led to improvement in cartilage biochemistry, as evidenced by MRI imaging. There is little other evidence, however, that strengthening or other exercise has an effect on joint structure.

Correction of Malalignment Malalignment in the frontal plane (varus-valgus) markedly increases the stress across the joint, which can lead to progression of disease and to pain and disability (Fig. 19-5). Correcting malalignment, either surgically or with bracing, may relieve pain in persons whose knees are maligned. Malalignment develops over years as a consequence of gradual anatomic alterations of the joint and bone, and correcting it is often very challenging. One way is with a fitted brace, which takes an often varus osteoarthritic knee and straightens it by putting valgus stress across the knee. Unfortunately, many patients are unwilling to wear a realigning knee brace, plus in patients with obese legs, braces may slip with usage and lose their realigning effect. They are indicated for willing patients who can learn to put them on correctly and on whom they do not slip.

Other ways of correcting malalignment across the knee include the use of orthotics in footwear. Unfortunately, while they may have modest effects on knee alignment, trials have heretofore not demonstrated efficacy of a lateral wedge orthotic vs. placebo wedges.

Pain from the patellofemoral compartment of the knee can be caused by tilting of the patella or patellar malalignment with the patella riding laterally (or less often, medially) in the femoral trochlear groove. Using a brace to realign the patella, or tape to pull the patella

back into the trochlear sulcus or reduce its tilt, has been shown, when compared to placebo taping in clinical trials, to lessen patellofemoral pain. However, patients may find it difficult to apply tape, and skin irritation from the tape is common. Commercial patellar braces may be a solution, but they have not been tested.

While their effect on malalignment is questionable, neoprene sleeves pulled to cover the knee lessen pain and are easy to use and popular among patients. The explanation for their therapeutic effect on pain is unclear.

In patients with knee OA, acupuncture produces modest pain relief compared to placebo needles and may be an adjunctive treatment.

PHARMACOTHERAPY While nonpharmacologic approaches to therapy constitute its mainstay, pharmacotherapy serves an important adjunctive role in OA treatment. Available drugs are administered using oral, topical, and intraarticular routes.

Acetaminophen, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), and COX-2 Inhibitors Acetaminophen (paracetamol) is the initial analgesic of choice for patients with OA in knee, hip, or hands. For some patients, it is adequate to control symptoms, in which case more toxic drugs such as NSAIDs can be avoided. Doses up to 1 g 3 times daily can be used to a maximum of 3000 mg per day (Table 19-1).

NSAIDs are the most popular drugs to treat osteoarthritic pain. They can be administered either topically or orally. In clinical trials, oral NSAIDs produce ~30% greater improvement in pain than high-dose acetaminophen. Occasional patients treated with NSAIDs experience dramatic pain relief, whereas others experience little improvement. Initially, NSAIDs should be administered topically or taken orally on an "as needed" basis because side effects are less frequent with low intermittent doses, which may be highly efficacious. If occasional medication use is insufficiently effective, then daily treatment may be indicated, with an anti-inflammatory dose selected (Table 19-1). Patients should be reminded to take low-dose aspirin and ibuprofen at different times to eliminate a drug interaction.

NSAIDs taken orally have substantial and frequent side effects, the most common of which is upper gastrointestinal toxicity, including dyspepsia, nausea, bloating,

TABLE 19-1

PHARMACOLOGIC TREATMENT FOR OSTEOARTHRITIS

TREATMENT	DOSAGE	COMMENTS
Acetaminophen	Up to 1 g tid (maximum 3000 mg per day)	Prolongs half-life of warfarin Dose related liver injury
Oral NSAIDs and COX-2 inhibitors[a] Naproxen Salsalate Ibuprofen	 375–500 mg bid 1500 mg bid 600–800 mg 3–4 times a day	Take with food. Increased risk of myocardial infarction and stroke for some NSAIDs and especially COX-2 inhibitors. High rates of gastrointestinal side effects, including ulcers and bleeding, occur. Patients at high risk for gastrointestinal side effects should also take either a proton pump inhibitor or misoprostol.[b] There is an increased gastrointestinal side effects or bleeding when taken with acetylsalicylic acid. Can also cause edema and renal insufficiency.
Topical NSAIDs Diclofenac Na 1% gel	 4gm qid (for knees)	Rub onto joint. Few systemic side effects. Skin irritation common.
Opiates	Various	Common side effects include dizziness, sedation, nausea or vomiting, dry mouth, constipation, urinary retention, and pruritis. Respiratory and central nervous system depression can occur.
Capsaicin	0.025–0.075% cream 3–4 times a day	Can irritate mucous membranes.
Intraarticular injections Steroids Hyaluronans	 Varies from 3–5 weekly injections depending on preparation	Mild to moderate pain at injection site. Controversy exists re: efficacy.

[a]COX-2, cyclooxygenase 2; NSAIDs, nonsteroidal anti-inflammatory drugs.
[b]Patients at high risk include those with previous gastrointestinal events, persons ≥60 years, and persons taking glucocorticoids. Trials have shown the efficacy of proton pump inhibitors and misoprostol in the prevention of ulcers and bleeding. Misoprostol is associated with a high rate of diarrhea and cramping; therefore, proton pump inhibitors are more widely used to reduce NSAID-related gastrointestinal symptoms.
Source: Adapted from DT Felson: N Engl J Med 354:841, 2006.

gastrointestinal bleeding, and ulcer disease. Some 30–40% of patients experience upper gastrointestinal (GI) side effects so severe as to require discontinuation of medication. To minimize the risk of nonsteroidal-related GI side effects, patients should not take two NSAIDs, and should take medications after food; if risk is high, patients should take a gastroprotective agent, such as a proton pump inhibitor. Certain oral agents are safer to the stomach than others including nonacetylated salicylates and nabumetone. Major NSAID-related GI side effects can occur in patients who do not complain of upper GI symptoms. In one study of patients hospitalized for GI bleeding, 81% had no premonitory symptoms.

Because of the increased rates of cardiovascular events associated with cyclooxygenase 2 (COX-2) inhibitors and with some conventional NSAIDs such as diclofenac, many of these drugs are not appropriate long-term treatment choices for older persons with osteoarthritis, especially those at high risk of heart disease or stroke. The American Heart Association has identified rofecoxib and all other COX-2 inhibitors as putting patients at high risk, although low doses of celecoxib, such as 200 mg/d, may not be associated with an elevation of risk. The only conventional NSAID that appears safe from a cardiovascular perspective is naproxen, but it does have gastrointestinal toxicity.

There are other common side effects of NSAIDs, including the tendency to develop edema, because of prostaglandin inhibition of afferent blood supply to glomeruli in the kidneys and, for similar reasons, a predilection toward reversible renal insufficiency. Blood pressure may increase modestly in some NSAID-treated patients.

With the approval by the U.S. Food and Drug Administration of topical diclofenac and the availability of these agents in Europe, clinicians have a choice of administration modality for anti-inflammatory drugs. NSAIDs can be placed into a gel or topical solution with another chemical modality that enhances penetration of the skin barrier. When absorbed through the skin, plasma concentrations are an order of magnitude lower than with the same amount of drug administered orally or parenterally. However, when these drugs are administered topically in proximity to a superficial joint, (knees, hands, but not hips), the drug can be found in joint tissues such as the synovium and cartilage. Trial results have varied but generally have found that topical NSAIDs are slightly less efficacious than oral agents, but have far fewer gastrointestinal and systemic side effects. Unfortunately, topical NSAIDs often cause local skin irritation where the medication is applied, inducing redness, burning or itching in up to 40 percent of patients (see Table 19-1).

Intraarticular Injections: Glucocorticoids and Hyaluronic Acid Since synovial inflammation is likely to be a major cause of pain in patients with OA, local anti-inflammatory treatments administered intraarticularly may be effective in ameliorating pain, at least temporarily. Glucocorticoid injections provide such efficacy, but work better than placebo injections for only 1 or 2 weeks. This may be because the disease remains mechanically driven and, when a person begins to use the joint, the loading factors that induce pain return. Glucocorticoid injections are useful to get patients over acute flares of pain and may be especially indicated if the patient has coexistent OA and crystal deposition disease, especially from calcium pyrophosphate dihydrate crystals (Chap. 20). There is no evidence that repeated glucocorticoid injections into the joint are dangerous.

Hyaluronic acid injections can be given for treatment of symptoms in knee and hip OA, but there is controversy as to whether they have efficacy vs. placebo (Table 19-1).

Optimal therapy for OA is often achieved by trial and error, with each patient having idiosyncratic responses to specific treatments. When medical therapies have failed and the patient has an unacceptable reduction in their quality of life and ongoing pain and disability, then at least for knee and hip OA, total joint arthroplasty is indicated.

SURGERY For knee OA, several operations are available. Among the most popular surgeries, at least in the United States, is arthroscopic debridement and lavage. Randomized trials evaluating this operation have showed that its efficacy is no greater than that of sham surgery or no treatment for relief of pain or disability. Even mechanical symptoms such as buckling, which are extremely common in patients with knee OA, do not respond to arthroscopic debridement. Arthroscopic meniscectomy is indicated for acute meniscal tears in which symptoms such as locking and acute pain are clearly related temporally to a knee injury that produced the tear.

For patients with knee OA isolated to the medial compartment, operations to realign the knee to lessen medial loading can relieve pain. These include a high tibial osteotomy, in which the tibia is broken just below the tibial plateau and realigned so as to load the lateral, nondiseased compartment, or a unicompartmental replacement with realignment. Each surgery may provide the patient with years of pain relief before they require a total knee replacement.

Ultimately, when the patient with knee or hip OA has failed medical treatment modalities and remains in pain, with limitations of physical function that compromise the quality of life, the patient should be referred for total knee or hip arthroplasty. These are highly efficacious

operations that relieve pain and improve function in the vast majority of patients. Currently failure rates are ~1% per year, although these rates are higher in obese patients. The chance of surgical success is greater in centers where at least 25 such operations are performed yearly or with surgeons who perform multiple operations annually. The timing of knee or hip replacement is critical. If the patient suffers for many years until their functional status has declined substantially, with considerable muscle weakness, postoperative functional status may not improve to a level achieved by others who underwent operation earlier in their disease course.

Cartilage Regeneration Chondrocyte transplantation has not been found to be efficacious in OA, perhaps because OA includes pathology of joint mechanics, which is not corrected by chondrocyte transplants. Similarly, abrasion arthroplasty (chondroplasty) has not been well studied for efficacy in OA, but it produces fibrocartilage in place of damaged hyaline cartilage. Both of these surgical attempts to regenerate and reconstitute articular cartilage may be more likely to be efficacious early in disease when joint malalignment and many of the other noncartilage abnormalities that characterize OA have not yet developed.

CHAPTER 20

GOUT AND OTHER CRYSTAL-ASSOCIATED ARTHROPATHIES

H. Ralph Schumacher ■ Lan X. Chen

The use of polarizing light microscopy during synovial fluid analysis in 1961 by McCarty and Hollander and the subsequent application of other crystallographic techniques, such as electron microscopy, energy-dispersive elemental analysis, and x-ray diffraction, have allowed investigators to identify the roles of different microcrystals, including monosodium urate (MSU), calcium pyrophosphate dihydrate (CPPD), calcium apatite (apatite), and calcium oxalate (CaOx), in inducing acute or chronic arthritis or periarthritis. The clinical events that result from deposition of MSU, CPPD, apatite, and CaOx have many similarities but also have important differences. Before the use of crystallographic techniques in rheumatology, much of what was considered to be gouty arthritis in fact was not. Because of often similar clinical presentations, the need to perform synovial fluid analysis to distinguish the type of crystal involved must be emphasized. Polarized light microscopy alone can identify most typical crystals; apatite, however, is an exception. Aspiration and analysis of effusions are also important to assess the possibility of infection. Apart from the identification of specific microcrystalline materials or organisms, synovial fluid characteristics in crystal-associated diseases are nonspecific, and synovial fluid can be inflammatory or noninflammatory. A list of possible musculoskeletal manifestations of crystal-associated arthritis is shown in Table 20-1.

TABLE 20-1

MUSCULOSKELETAL MANIFESTATIONS OF CRYSTAL-INDUCED ARTHRITIS	
Acute mono- or polyarthritis	Destructive arthropathies
Bursitis	Pseudo-rheumatoid arthritis
Tendinitis	Pseudo-ankylosing spondylitis
Enthesitis	Spinal stenosis
Tophaceous deposits	Crowned dens syndrome
Peculiar type of osteoarthritis	Carpal tunnel syndrome
Synovial osteochondromatosis	Tendon rupture

GOUT

Gout is a metabolic disease that most often affects middle-aged to elderly men and postmenopausal women. It results from an increased body pool of urate with hyperuricemia. It typically is characterized by episodic acute and chronic arthritis caused by deposition of MSU crystals in joints and connective tissue tophi and the risk for deposition in kidney interstitium or uric acid nephrolithiasis.

ACUTE AND CHRONIC ARTHRITIS

Acute arthritis is the most common early clinical manifestation of gout. Usually, only one joint is affected initially, but polyarticular acute gout can occur in subsequent episodes. The metatarsophalangeal joint of the first toe often is involved, but tarsal joints, ankles, and knees also are affected commonly. Especially in elderly patients or in advanced disease, finger joints may be involved. Inflamed Heberden's or Bouchard's nodes may be a first manifestation of gouty arthritis. The first episode of acute gouty arthritis frequently begins at night with dramatic joint pain and swelling. Joints rapidly become warm, red, and tender, with a clinical appearance that often mimics that of cellulitis. Early attacks tend to subside spontaneously within 3–10 days, and most patients have intervals of varying

length with no residual symptoms until the next episode. Several events may precipitate acute gouty arthritis: dietary excess, trauma, surgery, excessive ethanol ingestion, hypouricemic therapy, and serious medical illnesses such as myocardial infarction and stroke.

After many acute mono- or oligoarticular attacks, a proportion of gouty patients may present with a chronic nonsymmetric synovitis, causing potential confusion with rheumatoid arthritis (Chap. 6). Less commonly, chronic gouty arthritis will be the only manifestation, and, more rarely, the disease will manifest only as periarticular tophaceous deposits in the absence of synovitis. Women represent only 5–20% of all patients with gout. Premenopausal gout is rare; it is seen mostly in individuals with a strong family history of gout. Kindreds of precocious gout in young females caused by decreased renal urate clearance and renal insufficiency have been described. Most women with gouty arthritis are postmenopausal and elderly, have osteoarthritis and arterial hypertension that cause mild renal insufficiency, and usually are receiving diuretics.

Laboratory diagnosis

Even if the clinical appearance strongly suggests gout, the presumptive diagnosis ideally should be confirmed by needle aspiration of acutely or chronically involved joints or tophaceous deposits. Acute septic arthritis, several of the other crystalline-associated arthropathies, palindromic rheumatism, and psoriatic arthritis may present with similar clinical features. During acute gouty attacks, needle-shaped MSU crystals typically are seen both intracellularly and extracellularly **(Fig. 20-1)**. With compensated polarized light these crystals are brightly birefringent with negative elongation. Synovial fluid leukocyte counts are elevated from 2000 to 60,000/μL. Effusions appear cloudy due to the increased numbers of leukocytes. Large amounts of crystals occasionally produce a thick pasty or chalky joint fluid. Bacterial infection can coexist with urate crystals in synovial fluid; if there is any suspicion of septic arthritis, joint fluid must be cultured.

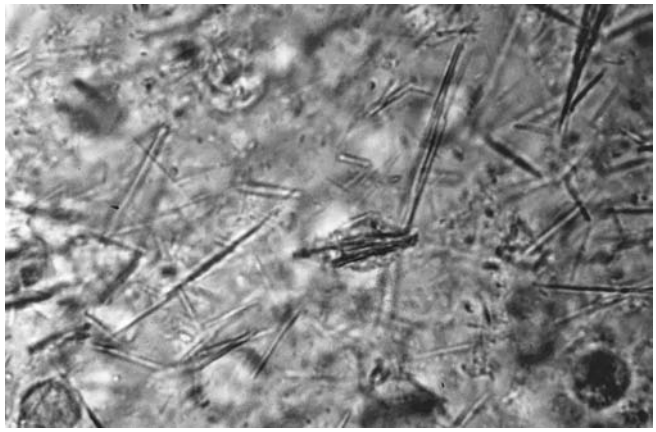


FIGURE 20-1
Extracellular and intracellular monosodium urate crystals, as seen in a fresh preparation of synovial fluid, illustrate needle- and rod-shaped crystals. These crystals are strongly negative birefringent crystals under compensated polarized light microscopy; 400x.

MSU crystals also can often be demonstrated in the first metatarsophalangeal joint and in knees not acutely involved with gout. Arthrocentesis of these joints is a useful technique to establish the diagnosis of gout between attacks.

Serum uric acid levels can be normal or low at the time of an acute attack, as inflammatory cytokines can be uricosuric and effective initiation of hypouricemic therapy can precipitate attacks. This limits the value of serum uric acid determinations for the diagnosis of gout. Nevertheless, serum urate levels are almost always elevated at some time and are important to use to follow the course of hypouricemic therapy. A 24-h urine collection for uric acid can, in some cases, be useful in assessing the risk of stones, elucidating overproduction or underexcretion of uric acid, and deciding whether it may be appropriate to use a uricosuric therapy. Excretion of >800 mg of uric acid per 24 h on a regular diet suggests that causes of overproduction of purine should be considered. Urinalysis, serum creatinine, hemoglobin, white blood cell (WBC) count, liver function tests, and serum lipids should be obtained because of possible pathologic sequelae of gout and other associated diseases requiring treatment and as baselines because of possible adverse effects of gout treatment.

Radiographic features

Early in the disease radiographic studies may only confirm clinically evident swelling. Cystic changes, well-defined erosions with sclerotic margins (often with overhanging bony edges), and soft tissue masses are characteristic features of advanced chronic tophaceous gout. Ultrasound, CT and MRI are being studied and are likely to become more sensitive for early changes.

TREATMENT Gout

ACUTE GOUTY ARTHRITIS The mainstay of treatment during an acute attack is the administration of anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or glucocorticoids. NSAIDs are used most often in individuals without complicating comorbid conditions. Both colchicine and

NSAIDs may be poorly tolerated and dangerous in the elderly and in the presence of renal insufficiency and gastrointestinal disorders. This was repeated later. Ice pack applications and rest of the involved joints can be helpful. Colchicine given orally is a traditional and effective treatment if used early in an attack. One useful regimen is one 0.6-mg tablet given every 8 h with subsequent tapering. This is generally better tolerated than the formerly advised hourly regimen. The drug must be stopped promptly at the first sign of loose stools, and symptomatic treatment must be given for the diarrhea. Intravenous colchicine has been taken off the market. NSAIDs given in full anti-inflammatory doses are effective in ~90% of patients, and the resolution of signs and symptoms usually occurs in 5–8 days. The most effective drugs are any of those with a short half-life and include indomethacin, 25–50 mg tid; naproxen, 500 mg bid; ibuprofen, 800 mg tid; and diclofenac, 50 mg tid. Glucocorticoids given IM or orally, for example, prednisone, 30–50 mg/d as the initial dose and gradually tapered with the resolution of the attack, can be effective in polyarticular gout. For a single joint or a few involved joints intraarticular triamcinolone acetonide, 20–40 mg, or methylprednisolone, 25–50 mg, have been effective and well tolerated. Based on recent evidence on the essential role of the inflammasome and interleukin 1 β (IL-1β) in acute gout, anakinra has been used and other inhibitors of IL-1β are under investigation.

HYPOURICEMIC THERAPY Ultimate control of gout requires correction of the basic underlying defect: the hyperuricemia. Attempts to normalize serum uric acid to <300–360 μmol/L (5.0–6.0 mg/dL) to prevent recurrent gouty attacks and eliminate tophaceous deposits entail a commitment to long-term hypouricemic regimens and medications that generally are required for life. Hypouricemic therapy should be considered when, as in most patients, the hyperuricemia cannot be corrected by simple means (control of body weight, low-purine diet, increase in liquid intake, limitation of ethanol use, decreased use of fructose-containing foods and beverages, and avoidance of diuretics). The decision to initiate hypouricemic therapy usually is made taking into consideration the number of acute attacks (urate lowering may be cost-effective after two attacks), serum uric acid levels (progression is more rapid in patients with serum uric acid >535 μmol/L [>9.0 mg/dL]), the patient's willingness to commit to lifelong therapy, or the presence of uric acid stones. Urate-lowering therapy should be initiated in any patient who already has tophi or chronic gouty arthritis. Uricosuric agents such as probenecid can be used in patients with good renal function who underexcrete uric acid, with <600 mg in a 24-h urine sample. Urine volume must be maintained by ingestion of 1500 mL of water every day. Probenecid can be started at a dose of 250 mg twice daily and increased gradually as needed up to 3 g per day to maintain a serum uric acid level <360 μmol/L (6 mg/dL). Probenecid is generally not effective in patients with serum creatinine levels >177 μmol/L (2 mg/dL). These patients may require allopurinol or benzbromarone (not available in the United States). Benzbromarone is another uricosuric drug that is more effective in patients with renal failure. Some agents used to treat common comorbidities, including losartan, fenofibrate, and amlodipine, have some mild uricosuric effects.

The xanthine oxidase inhibitor allopurinol is by far the most commonly used hypouricemic agent and is the best drug to lower serum urate in overproducers, urate stone formers, and patients with renal disease. It can be given in a single morning dose, 100–300 mg initially and increasing up to 800 mg if needed. In patients with chronic renal disease, the initial allopurinol dose should be lower and adjusted depending on the serum creatinine concentration; for example, with a creatinine clearance of 10 mL/min, one generally would use 100 mg every other day. Doses can be increased gradually to reach the target urate level of 6 mg/dL; however, more studies are needed to provide exact guidance. Toxicity of allopurinol has been recognized increasingly in patients who use thiazide diuretics and patients allergic to penicillin and ampicillin. The most serious side effects include life-threatening toxic epidermal necrolysis, systemic vasculitis, bone marrow suppression, granulomatous hepatitis, and renal failure. Patients with mild cutaneous reactions to allopurinol can reconsider the use of a uricosuric agent, undergo an attempt at desensitization to allopurinol, or take febuxostat, a chemically unrelated specific xanthine oxidase inhibitor. Febuxostat is approved at 40 or 80 mg once a day and does not require dose adjustment in mild to moderate renal disease. Patients can also pay increased attention to diet and should be aware of new alternative agents (see next). Urate-lowering drugs are generally not initiated during acute attacks, but after the patient is stable and low-dose colchicine has been initiated to decrease the risk of the flares that often occur with urate lowering. Colchicine anti-inflammatory prophylaxis in doses of 0.6 mg one to two times daily should be given along with the hypouricemic therapy until the patient is normouricemic and without gouty attacks for 6 months or as long as tophi are present. Colchicine should not be used in dialysis patients and is given in lower doses in patients with renal disease or with P gylcoprotein or CYP3A4 inhibitors such as clarithromycin that can increase toxicity of colchicine. Pegloticase is a new urate-lowering biologic agent that can be effective in patients allergic to or failing xanthine oxidase inhibitors who have severe tophaceous gout. Pegloticase is associated with antibody formation linked to loss of response

and development of severe infusion reactions. Uric acid levels should be measured prior to each infusion with discontinuation of peglotidase for uric acid levels >6 mg/dL. Pegloticase should not be used concurrently with allopurinol or febuxostat as this may mask the rise in uric acid and its ability to be use this measure as a heralding feature for a possible infusion reaction.. New uricosurics are undergoing investigation.

CPPD DEPOSITION DISEASE

PATHOGENESIS

The deposition of CPPD crystals in articular tissues is most common in the elderly, occurring in 10–15% of persons age 65–75 years and 30–50% of those >85 years. In most cases, this process is asymptomatic and the cause of CPPD deposition is uncertain. Because >80% of patients are >60 years and 70% have preexisting joint damage from other conditions, it is likely that biochemical changes in aging or diseased cartilage favors crystal nucleation. In patients with CPPD arthritis there is increased production of inorganic pyrophosphate and decreased levels of pyrophosphatases in cartilage extracts. Mutations in the *ANKH* gene, as described in both familial and sporadic cases, can increase elaboration and extracellular transport of pyrophosphate. The increase in pyrophosphate production appears to be related to enhanced activity of ATP pyrophosphohydrolase and 5′-nucleotidase, which catalyze the reaction of ATP to adenosine and pyrophosphate. This pyrophosphate could combine with calcium to form CPPD crystals in matrix vesicles or on collagen fibers. There are decreased levels of cartilage glycosaminoglycans that normally inhibit and regulate crystal nucleation. High activities of transglutaminase enzymes also may contribute to the deposition of CPPD crystals.

Release of CPPD crystals into the joint space is followed by the phagocytosis of those crystals by monocyte-macrophages and neutrophils, which respond by releasing chemotactic and inflammatory substances and, as with MSU crystals, activate the inflammasome.

A minority of patients with CPPD arthropathy have metabolic abnormalities or hereditary CPPD disease **(Table 20-2)**. These associations suggest that a variety of different metabolic products may enhance CPPD deposition either by directly altering cartilage or by inhibiting inorganic pyrophosphatases. Included among these conditions are hyperparathyroidism, hemochromatosis, hypophosphatasia, hypomagnesemia, and possibly myxedema. The presence of CPPD arthritis in individuals <50 years old should lead to consideration of these metabolic disorders (Table 20-2) and inherited forms of disease, including those identified in a variety of ethnic groups. Genomic DNA studies performed on different kindreds have shown a possible location of genetic defects on chromosome 8q or on chromosome 5p in a region that expresses the gene of the membrane pyrophosphate channel (*ANKH* gene). As noted above, mutations described in the *ANKH* gene in kindreds with CPPD arthritis can increase extracellular pyrophosphate and induce CPPD crystal formation. Investigation of younger patients with CPPD deposition should include inquiry for evidence of familial aggregation and evaluation of serum calcium, phosphorus, alkaline phosphatase, magnesium, serum iron, and transferrin.

TABLE 20-2

CONDITIONS ASSOCIATED WITH CALCIUM PYROPHOSPHATE DIHYDRATE DISEASE
Aging
Disease-associated
Primary hyperparathyroidism
Hemochromatosis
Hypophosphatasia
Hypomagnesemia
Chronic gout
Postmeniscectomy
Gitelman's syndrome
Epiphyseal dysplasias

CLINICAL MANIFESTATIONS

CPPD arthropathy may be asymptomatic, acute, subacute, or chronic or may cause acute synovitis superimposed on chronically involved joints. Acute CPPD arthritis originally was termed *pseudogout* by McCarty and co-workers because of its striking similarity to gout. Other clinical manifestations of CPPD deposition include (1) induction or enhancement of peculiar forms of osteoarthritis, (2) induction of severe destructive disease that may radiographically mimic neuropathic arthritis, (3) production of symmetric synovitis that is clinically similar to rheumatoid arthritis and sometimes seen in familial forms with early onset, (4) intervertebral disk and ligament calcification with restriction of spine mobility that mimics ankylosing spondylitis (also seen in hereditary forms), (5) spinal stenosis (most commonly seen in the elderly), and (6) rarely periarticular tophus-like nodules.

The knee is the joint most frequently affected in CPPD arthropathy. Other sites include the wrist, shoulder, ankle, elbow, and hands. The temporomandibular joint and ligamentum flavum of the spinal canal may be involved. Clinical and radiographic evidence indicates that CPPD deposition is polyarticular in at least two-thirds of patients. When the clinical picture resembles that of slowly progressive osteoarthritis, diagnosis may be difficult. Joint distribution may provide important clues suggesting CPPD disease. For example, primary osteoarthritis less often involves a metacarpophalangeal, wrist,

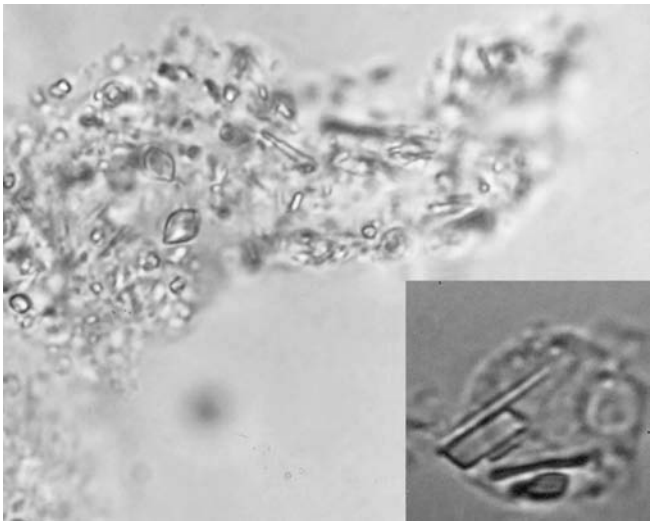


FIGURE 20-2
Intracellular and extracellular calcium pyrophosphate dihydrate crystals, as seen in a fresh preparation of synovial fluid, illustrate rectangular, rod-shaped, and rhomboid crystals that are weakly positive birefringent crystals (compensated polarized light microscopy; 400x).

elbow, shoulder, or ankle joints. If radiographs reveal punctate and/or linear radiodense deposits in fibrocartilaginous joint menisci or articular hyaline cartilage (*chondrocalcinosis*), the diagnostic likelihood of CPPD disease is further increased. *Definitive diagnosis* requires demonstration of typical rhomboid or rodlike crystals in synovial fluid or articular tissue **(Fig. 20-2)**. In the absence of joint effusion or indications to obtain a synovial biopsy, chondrocalcinosis is presumptive of CPPD deposition. One exception is chondrocalcinosis due to CaOx in some patients with chronic renal failure.

Acute attacks of CPPD arthritis may be precipitated by trauma. Rapid diminution of serum calcium concentration, as may occur in severe medical illness or after surgery (especially parathyroidectomy), can also lead to pseudogout attacks.

In as many as 50% of cases, episodes of CPPD-induced inflammation are associated with low-grade fever and, on occasion, temperatures as high as 40°C (104°F). Whether or not radiographic proof of chondrocalcinosis is evident in the involved joint(s), synovial fluid analysis with microbial cultures is essential to rule out the possibility of infection. In fact, infection in a joint with any microcrystalline deposition process can lead to crystal shedding and subsequent synovitis from both crystals and microorganisms. Synovial fluid in acute CPPD disease has inflammatory characteristics. The leukocyte count can range from several thousand cells to 100,000 cells/μL, with the mean being about 24,000 cells/μL and the predominant cell being the neutrophil. Polarized light microscopy usually reveals rhomboid, square, or rodlike crystals with weak positive birefringence inside tissue fragments and fibrin clots and in neutrophils (Fig. 20-2). CPPD crystals may coexist with MSU and apatite in some cases.

TREATMENT **CPPD Deposition Disease**

Untreated acute attacks may last a few days to as long as a month. Treatment by joint aspiration and NSAIDs or by intraarticular glucocorticoid injection may result in return to prior status in ≤10 days. For patients with frequent recurrent attacks of pseudogout, daily prophylactic treatment with low doses of colchicine may be helpful in decreasing the frequency of the attacks. Severe polyarticular attacks usually require short courses of glucocorticoids or, as recently reported, an IL-1β antagonist, anakinra. Unfortunately, there is no effective way to remove CPPD deposits from cartilage and synovium. Uncontrolled studies suggest that the administration of antimalarial agents or even methotrexate may be helpful in controlling persistent synovitis. Patients with progressive destructive large-joint arthropathy may require joint replacement.

CALCIUM APATITE DEPOSITION DISEASE

PATHOGENESIS

Apatite is the primary mineral of normal bone and teeth. Abnormal accumulation of basic calcium phosphates, largely carbonate substituted apatite, can occur in areas of tissue damage (dystrophic calcification), hypercalcemic or hyperparathyroid states (metastatic calcification), and certain conditions of unknown cause **(Table 20-3)**. In chronic renal failure, hyperphosphatemia can contribute to extensive apatite deposition both in and around joints. Familial aggregation is rarely seen; no association with *ANKH* mutations has been described thus far. Apatite crystals are deposited primarily on matrix vessels. Incompletely understood alterations in matrix proteoglycans, phosphatases, hormones, and cytokines probably can influence crystal formation.

Apatite aggregates are commonly present in synovial fluid in an extremely destructive chronic arthropathy of the elderly that occurs most often in the shoulders (Milwaukee shoulder) and in a similar process in hips, knees, and erosive osteoarthritis of fingers. Joint destruction is associated with damage to cartilage and supporting structures, leading to instability and deformity. Progression tends to be indolent, and synovial fluid leukocyte counts are usually <2000/μL. Symptoms range from minimal to severe pain and disability that may lead to joint replacement surgery. Whether severely affected patients merely represent an extreme synovial tissue response to the apatite crystals that are so common in

TABLE 20-3

CONDITIONS ASSOCIATED WITH APATITE DEPOSITION DISEASE
Aging
Osteoarthritis
Hemorrhagic shoulder effusions in the elderly (Milwaukee shoulder)
Destructive arthropathy
Tendinitis, bursitis
Tumoral calcinosis (sporadic cases)
Disease-associated
Hyperparathyroidism
Milk-alkali syndrome
Renal failure/long-term dialysis
Connective tissue diseases (e.g., systemic sclerosis, idiopathic myositis, SLE)
Heterotopic calcification after neurologic catastrophes (e.g., stroke, spinal cord injury)
Heredity
Bursitis, arthritis
Tumoral calcinosis
Fibrodysplasia ossificans progressiva

Abbreviation: SLE, systemic lupus erythematosus.

osteoarthritis is uncertain. Synovial lining cell or fibroblast cultures exposed to apatite (or CPPD) crystals can undergo mitosis and markedly increase the release of prostaglandin E_2 and cytokines and also collagenases and neutral proteases, underscoring the destructive potential of abnormally stimulated synovial lining cells.

CLINICAL MANIFESTATIONS

Periarticular or articular deposits may occur and may be associated with acute reversible inflammation and/or chronic damage to the joint capsule, tendons, bursa, or articular surfaces. The most common sites of apatite deposition include bursae and tendons in and/or around the knees, shoulders, hips, and fingers. Clinical manifestations include asymptomatic radiographic abnormalities, acute synovitis, bursitis, tendinitis, and chronic destructive arthropathy. Although the true incidence of apatite arthritis is not known, 30–50% of patients with osteoarthritis have apatite microcrystals in their synovial fluid. Such crystals frequently can be identified in clinically stable osteoarthritic joints, but they are more likely to come to attention in persons experiencing acute or subacute worsening of joint pain and swelling. The synovial fluid leukocyte count in apatite arthritis is usually low (<2000/μL) despite dramatic symptoms, with predominance of mononuclear cells.

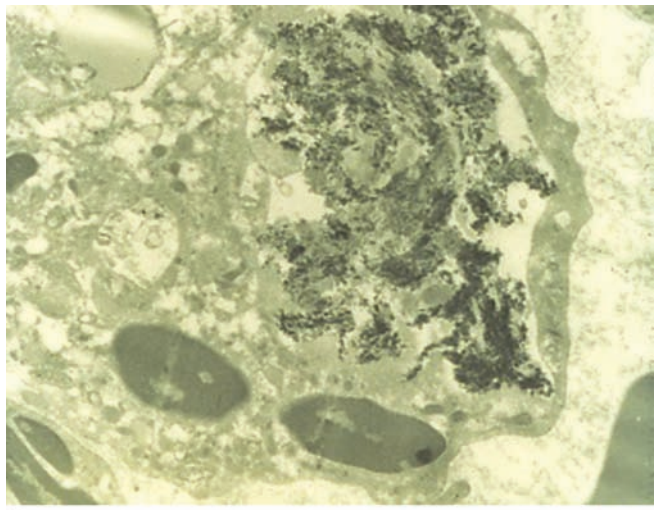
DIAGNOSIS

Intra- and/or periarticular calcifications with or without erosive, destructive, or hypertrophic changes may be seen on radiographs (Fig. 20-3). They should be distinguished from the linear calcifications typical of CPPD deposition disease.

Definitive diagnosis of apatite arthropathy, also called basic calcium phosphate disease, depends on identification of crystals from synovial fluid or tissue (Fig. 20-3). Individual crystals are very small and can be seen only by electron microscopy. Clumps of crystals may appear as 1- to 20-μm shiny intra- or extracellular nonbirefringent globules or aggregates that stain purplish



A



B

FIGURE 20-3

A. **Radiograph showing calcification** due to apatite crystals surrounding an eroded joint. ***B.*** An electron micrograph demonstrates dark needle-shaped apatite crystals within a vacuole of a synovial fluid mononuclear cell (30,000x).

with Wright's stain and bright red with alizarin red S. Tetracycline binding is under investigation as a labeling alternative. Absolute identification depends on electron microscopy with energy-dispersive elemental analysis, x-ray diffraction, infrared spectroscopy, or Raman microspectroscopy, but they usually are not required in clinical diagnosis.

TREATMENT Calcium Apatite Deposition Disease

Treatment of apatite arthritis or periarthritis is nonspecific. Acute attacks of bursitis or synovitis may be self-limiting, resolving in days to several weeks. Aspiration of effusions and the use of either NSAIDs or oral colchicine for 2 weeks or intra- or periarticular injection of a depot glucocorticoid appear to shorten the duration and intensity of symptoms. Local injection of disodium ethylenediaminetetraacetic acid (EDTA) was effective in one study of calcific tendinitis at the shoulder. Periarticular apatite deposits may be resorbed with resolution of attacks. Agents to lower serum phosphate levels may lead to resorption of deposits in renal failure patients receiving hemodialysis. In patients with underlying severe destructive articular changes, response to medical therapy is usually less rewarding.

CaOx DEPOSITION DISEASE

PATHOGENESIS

Primary oxalosis is a rare hereditary metabolic disorder. Enhanced production of oxalic acid may result from at least two different enzyme defects, leading to hyperoxalemia and deposition of calcium oxalate crystals in tissues. Nephrocalcinosis, renal failure, and death usually occur before age 20. Acute and/or chronic CaOx arthritis and periarthritis may complicate primary oxalosis during later years of illness.

Secondary oxalosis is more common than the primary disorder. It is one of the many metabolic abnormalities that complicate end-stage renal disease. In chronic renal disease, calcium oxalate deposits have long been recognized in visceral organs, blood vessels, bones, and cartilage and are now known to be one of the causes of arthritis in chronic renal failure. Thus far, reported patients have been dependent on long-term hemodialysis or peritoneal dialysis, and many had received ascorbic acid supplements. Ascorbic acid is metabolized to oxalate, which is inadequately cleared in uremia and by dialysis. Such supplements usually are avoided in dialysis programs because of the risk of enhancing hyperoxalosis and its sequelae.

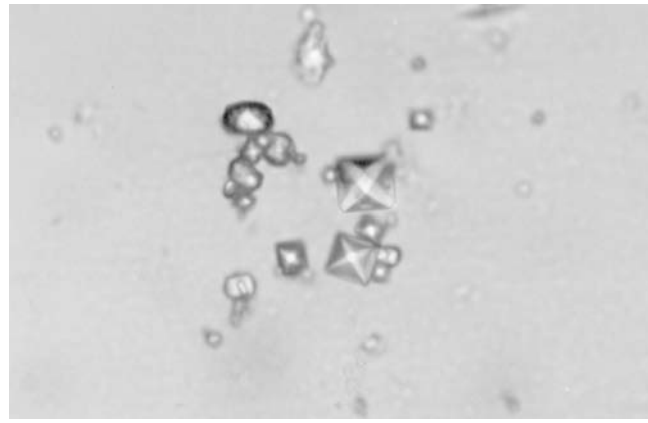


FIGURE 20-4
Bipyramidal and small polymorphic calcium oxalate crystals from synovial fluid are a classic finding in CaOx arthropathy (ordinary light microscopy; 400x).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

CaOx aggregates can be found in bone, articular cartilage, synovium, and periarticular tissues. From these sites, crystals may be shed, causing acute synovitis. Persistent aggregates of CaOx can, like apatite and CPPD, stimulate synovial cell proliferation and enzyme release, resulting in progressive articular destruction. Deposits have been documented in fingers, wrists, elbows, knees, ankles, and feet.

Clinical features of acute CaOx arthritis may not be distinguishable from those due to sodium urate, CPPD, or apatite. Radiographs may reveal chondrocalcinosis or soft tissue calcifications. CaOx-induced synovial effusions are usually noninflammatory, with <2000 leukocytes/μL, or mildly inflammatory. Neutrophils or mononuclear cells can predominate. CaOx crystals have a variable shape and variable birefringence to polarized light. The most easily recognized forms are bipyramidal, have strong birefringence **(Fig. 20-4)**, and stain with alizarin red S.

TREATMENT Calcium Oxalate Deposition Disease

Treatment of CaOx arthropathy with NSAIDs, colchicine, intraarticular glucocorticoids, and/or an increased frequency of dialysis has produced only slight improvement. In primary oxalosis, liver transplantation has induced a significant reduction in crystal deposits.

ACKNOWLEDGMENT

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CHAPTER 21

INFECTIOUS ARTHRITIS

Lawrence C. Madoff

Although *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and other bacteria are the most common causes of infectious arthritis, various mycobacteria, spirochetes, fungi, and viruses also infect joints **(Table 21-1)**. Since acute bacterial infection can destroy articular cartilage rapidly, all inflamed joints must be evaluated without delay to exclude noninfectious processes and determine appropriate antimicrobial therapy and drainage procedures.

Acute bacterial infection typically involves a single joint or a few joints. Subacute or chronic monarthritis or oligoarthritis suggests mycobacterial or fungal infection; episodic inflammation is seen in syphilis, Lyme disease, and the reactive arthritis that follows enteric infections and chlamydial urethritis. Acute polyarticular inflammation occurs as an immunologic reaction during the course of endocarditis, rheumatic fever, disseminated neisserial infection, and acute hepatitis B. Bacteria and viruses occasionally infect multiple joints, the former most commonly in persons with rheumatoid arthritis.

APPROACH TO THE PATIENT **Infectious Arthritis**

Aspiration of synovial fluidan essential element in the evaluation of potentially infected jointscan be performed without difficulty in most cases by the insertion of a large-bore needle into the site of maximal fluctuance or tenderness or by the route of easiest access. Ultrasonography or fluoroscopy may be used to guide aspiration of difficult-to-localize effusions of the hip and, occasionally, the shoulder and other joints. Normal synovial fluid contains <180 cells (predominantly mononuclear cells) per microliter. Synovial cell counts averaging 100,000/μL (range, 25,000–250,000/μL), with >90% neutrophils, are characteristic of acute bacterial infections. Crystal-induced, rheumatoid, and other noninfectious inflammatory arthritides usually are associated with <30,000–50,000 cells/μL; cell counts of 10,000–30,000/μL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections. Definitive diagnosis of an infectious process relies on identification of the pathogen in stained smears of synovial fluid, isolation of the pathogen from cultures of synovial fluid and blood, or detection of microbial nucleic acids and proteins by nucleic acid amplification (NAA)–based assays and immunologic techniques.

ACUTE BACTERIAL ARTHRITIS

Pathogenesis

Bacteria enter the joint from the bloodstream; from a contiguous site of infection in bone or soft tissue; or by direct inoculation during surgery, injection, animal or human bite, or trauma. In hematogenous infection, bacteria escape from synovial capillaries, which have no limiting basement membrane, and within hours provoke neutrophilic infiltration of the synovium. Neutrophils and bacteria enter the joint space; later, bacteria adhere to articular cartilage. Degradation of cartilage begins within 48 h as a result of increased intraarticular pressure, release of proteases and cytokines from chondrocytes and synovial macrophages, and invasion of the cartilage by bacteria and inflammatory cells. Histologic studies reveal bacteria lining the synovium and cartilage as well as abscessesextending into the synovium, cartilage, and, in severe cases, subchondral bone. Synovial proliferation results in the formation of a pannus over the cartilage, and thrombosis of inflamed synovial vessels develops. Bacterial factors that appear important in the pathogenesis of infective arthritis include various surface-associated adhesins in *S. aureus* that permit

TABLE 21-1

DIFFERENTIAL DIAGNOSIS OF ARTHRITIS SYNDROMES

ACUTE MONARTICULAR ARTHRITIS	CHRONIC MONARTICULAR ARTHRITIS	POLYARTICULAR ARTHRITIS
Staphylococcus aureus	*Mycobacterium tuberculosis*	*Neisseria meningitidis*
Streptococcus pneumoniae	Nontuberculous mycobacteria	*N. gonorrhoeae*
β-Hemolytic streptococci	*Borrelia burgdorferi*	Nongonococcal bacterial arthritis
Gram-negative bacilli	*Treponema pallidum*	Bacterial endocarditis
Neisseria gonorrhoeae	*Candida* species	*Candida* species
Candida species	*Sporothrix schenckii*	Poncet's disease (tuberculous rheumatism)
Crystal-induced arthritis	*Coccidioides immitis*	Hepatitis B virus
Fracture	*Blastomyces dermatitidis*	Parvovirus B19
Hemarthrosis	*Aspergillus species*	HIV
Foreign body	*Cryptococcus neoformans*	Human T-lymphotropic virus type I
Osteoarthritis	*Nocardia* species	Rubella virus
Ischemic necrosis	*Brucella* species	Arthropod-borne viruses
Monarticular rheumatoid arthritis	Legg-Calvé-Perthes disease	Sickle cell disease flare
	Osteoarthritis	Reactive arthritis
		Serum sickness
		Acute rheumatic fever
		Inflammatory bowel disease
		Systemic lupus erythematosus
		Rheumatoid arthritis/Still's disease
		Other vasculitides
		Sarcoidosis

adherence to cartilage and endotoxins that promote chondrocyte-mediated breakdown of cartilage.

Microbiology

The hematogenous route of infection is the most common route in all age groups, and nearly every bacterial pathogen is capable of causing septic arthritis. In infants, group B streptococci, gram-negative enteric bacilli, and *S. aureus* are the most common pathogens. Since the advent of the *Haemophilus influenzae* vaccine, the predominant causes among children <5 years of age have been *S. aureus*, *Streptococcus pyogenes* (group A *Streptococcus*), and (in some centers) *Kingella kingae*. Among young adults and adolescents, *N. gonorrhoeae* is the most commonly implicated organism. *S. aureus* accounts for most nongonococcal isolates in adults of all ages; gram-negative bacilli, pneumococci, and β-hemolytic streptococci,—particularly groups A and B—but also groups C, G, and F'are involved in up to one-third of cases in older adults, especially those with underlying comorbid illnesses.

Infections after surgical procedures or penetrating injuries are due most often to *S. aureus* and occasionally to other gram-positive bacteria or gram-negative bacilli. Infections with coagulase-negative staphylococci are unusual except after the implantation of prosthetic joints or arthroscopy. Anaerobic organisms, often in association with aerobic or facultative bacteria, are found after human bites and when decubitus ulcers or intraabdominal abscesses spread into adjacent joints. Polymicrobial infections complicate traumatic injuries with extensive contamination. Bites and scratches from cats and other animals may introduce *Pasteurella multocida* into joints, and bites from humans may introduce *Eikenella corrodens* or other components of the oral flora.

Nongonococcal bacterial arthritis

Epidemiology

Although hematogenous infections with virulent organisms such as *S. aureus*, *H. influenzae*, and pyogenic streptococci occur in healthy persons, there is an underlying host predisposition in many cases of septic arthritis. Patients with rheumatoid arthritis have the highest incidence

of infective arthritis (most often secondary to *S. aureus*) because of chronically inflamed joints; glucocorticoid therapy; and frequent breakdown of rheumatoid nodules, vasculitic ulcers, and skin overlying deformed joints. Diabetes mellitus, glucocorticoid therapy, hemodialysis, and malignancy all carry an increased risk of infection with *S. aureus* and gram-negative bacilli. Tumor necrosis factor inhibitors (etanercept and infliximab), which increasingly are used for the treatment of rheumatoid arthritis, predispose to mycobacterial infections and possibly to other pyogenic bacterial infections and could be associated with septic arthritis in this population. Pneumococcal infections complicate alcoholism, deficiencies of humoral immunity, and hemoglobinopathies. Pneumococci, *Salmonella* species, and *H. influenzae* cause septic arthritis in persons infected with HIV. Persons with primary immunoglobulin deficiency are at risk for mycoplasmal arthritis, which results in permanent joint damage if tetracycline and replacement therapy with IV immunoglobulin are not administered promptly. IV drug users acquire staphylococcal and streptococcal infections from their own flora and acquire pseudomonal and other gram-negative infections from drugs and injection paraphernalia.

Clinical manifestations

Some 90% of patients present with involvement of a single joint'most commonly the knee; less frequently the hip; and still less often the shoulder, wrist, or elbow. Small joints of the hands and feet are more likely to be affected after direct inoculation or a bite. Among IV drug users, infections of the spine, sacroiliac joints, and sternoclavicular joints **(Fig. 21-1)** are more common than infections of the appendicular skeleton. Polyarticular infection is most common among patients with rheumatoid arthritis and may resemble a flare of the underlying disease.

The usual presentation consists of moderate to severe pain that is uniform around the joint, effusion, muscle spasm, and decreased range of motion. Fever in the range of 38.3°–38.9°C (101°–102°F) and sometimes higher is common but may not be present, especially in persons with rheumatoid arthritis, renal or hepatic insufficiency, or conditions requiring immunosuppressive therapy. The inflamed, swollen joint is usually evident on examination except in the case of a deeply situated joint such as the hip, shoulder, or sacroiliac joint. Cellulitis, bursitis, and acute osteomyelitis, which may produce a similar clinical picture, should be distinguished from septic arthritis by their greater range of motion and less than circumferential swelling. A focus of extraarticular infection such as a boil or pneumonia should be sought. Peripheral-blood leukocytosis with a left shift and elevation of the erythrocyte sedimentation rate or C-reactive protein level are common.



FIGURE 21-1

Acute septic arthritis of the sternoclavicular joint. A man in his forties with a history of cirrhosis presented with a new onset of fever and lower neck pain. He had no history of IV drug use or previous catheter placement. Jaundice and a painful swollen area over his left sternoclavicular joint were evident on physical examination. Cultures of blood drawn at admission grew group B *Streptococcus*. The patient recovered after treatment with IV penicillin. (*Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.*)

Plain radiographs show evidence of soft tissue swelling, joint-space widening, and displacement of tissue planes by the distended capsule. Narrowing of the joint space and bony erosions indicate advanced infection and a poor prognosis. Ultrasound is useful for detecting effusions in the hip, and CT or MRI can demonstrate infections of the sacroiliac joint, the sternoclavicular joint, and the spine very well.

Laboratory findings

Specimens of peripheral blood and synovial fluid should be obtained before antibiotics are administered. Blood cultures are positive in up to 50–70% of *S. aureus* infections but are less frequently positive in infections due to other organisms. The synovial fluid is turbid, serosanguineous, or frankly purulent. Gram-stained smears confirm the presence of large numbers of neutrophils. Levels of total protein and lactate dehydrogenase in synovial fluid are elevated, and the glucose level is depressed; however, these findings are not specific for infection, and measurement of these levels is not necessary for diagnosis. The synovial fluid should be examined for crystals, because gout and pseudogout can resemble septic arthritis clinically, and infection and crystal-induced disease occasionally occur together. Organisms are seen on synovial fluid smears in nearly three-quarters of infections with *S. aureus* and streptococci and in 30–50% of infections due to gram-negative and other bacteria.

Cultures of synovial fluid are positive in >90% of cases. Inoculation of synovial fluid into bottles containing liquid media for blood cultures increases the yield of a culture, especially if the pathogen is a fastidious organism or the patient is taking an antibiotic. Although not yet widely available, NAA-based assays for bacterial DNA will be useful for the diagnosis of partially treated or culture-negative bacterial arthritis.

TREATMENT **Nongonococcal Bacterial Arthritis**

Prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity. Once samples of blood and synovial fluid have been obtained for culture, empirical antibiotics should be given that are directed against the bacteria visualized on smears or the pathogens that are likely in light of the patient's age and risk factors. Initial therapy should consist of IV administration of bactericidal agents; direct instillation of antibiotics into the joint is not necessary to achieve adequate levels in synovial fluid and tissue. An IV third-generation cephalosporin such as cefotaxime (1 g every 8 h) or ceftriaxone (1–2 g every 24 h) provides adequate empirical coverage for most community-acquired infections in adults when smears show no organisms. IV vancomycin (1 g every 12 h) is used if there are gram-positive cocci on the smear. If methicillin-resistant *S. aureus* is an unlikely pathogen (e.g., when it is not widespread in the community), either oxacillin or nafcillin (2 g every 4 h) should be given. In addition, an aminoglycoside or third-generation cephalosporin should be given to IV drug users or other patients in whom *Pseudomonas aeruginosa* may be the responsible agent.

Definitive therapy is based on the identity and antibiotic susceptibility of the bacteria isolated in culture. Infections due to staphylococci are treated with oxacillin, nafcillin, or vancomycin for 4 weeks. Pneumococcal and streptococcal infections due to penicillin-susceptible organisms respond to 2 weeks of therapy with penicillin G (2 million units IV every 4 h); infections caused by *H. influenzae* and by strains of *Streptococcus pneumoniae* that are resistant to penicillin are treated with cefotaxime or ceftriaxone for 2 weeks. Most enteric gram-negative infections can be cured in 3–4 weeks by a second- or third-generation cephalosporin given IV or by a fluoroquinolone such as levofloxacin (500 mg IV or PO every 24 h). *P. aeruginosa* infection should be treated for at least 2 weeks with a combination regimen of an aminoglycoside plus, either an extended-spectrum penicillin such as mezlocillin (3 g IV every 4 h) or an antipseudomonal cephalosporin such as ceftazidime (1 g IV every 8 h). If tolerated, this regimen is continued for an additional 2 weeks; alternatively, a fluoroquinolone such as ciprofloxacin (750 mg PO twice daily) is given by itself or with the penicillin or cephalosporin in place of the aminoglycoside.

Timely drainage of pus and necrotic debris from the infected joint is required for a favorable outcome. Needle aspiration of readily accessible joints such as the knee may be adequate if loculations or particulate matter in the joint does not prevent its thorough decompression. Arthroscopic drainage and lavage may be employed initially or within several days if repeated needle aspiration fails to relieve symptoms, decrease the volume of the effusion and the synovial white cell count, and clear bacteria from smears and cultures. In some cases, arthrotomy is necessary to remove loculations and debride infected synovium, cartilage, or bone. Septic arthritis of the hip is best managed with arthrotomy, particularly in young children, in whom infection threatens the viability of the femoral head. Septic joints do not require immobilization except for pain control before symptoms are alleviated by treatment. Weight bearing should be avoided until signs of inflammation have subsided, but frequent passive motion of the joint is indicated to maintain full mobility. Although addition of glucocorticoids to antibiotic treatment improves the outcome of *S. aureus* arthritis in experimental animals, no clinical trials have evaluated this approach in humans.

Gonococcal arthritis

Epidemiology

Although its incidence has declined in recent years, gonococcal arthritis has accounted for up to 70% of episodes of infectious arthritis in persons <40 years of age in the United States. Arthritis due to *N. gonorrhoeae* is a consequence of bacteremia arising from gonococcal infection or, more frequently, from asymptomatic gonococcal mucosal colonization of the urethra, cervix, or pharynx. Women are at greatest risk during menses and during pregnancy and overall are two to three times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis. Persons with complement deficiencies, especially of the terminal components, are prone to recurrent episodes of gonococcemia. Strains of gonococci that are most likely to cause DGI include those which produce transparent colonies in culture, have the type IA outer-membrane protein, or are of the AUH-auxotroph type.

Clinical manifestations and laboratory findings

The most common manifestation of DGI is a syndrome of fever, chills, rash, and articular symptoms. Small numbers of papules that progress to hemorrhagic pustules develop on the trunk and the extensor surfaces of the distal extremities. Migratory arthritis and tenosynovitis

of the knees, hands, wrists, feet, and ankles are prominent. The cutaneous lesions and articular findings are believed to be the consequence of an immune reaction to circulating gonococci and immune-complex deposition in tissues. Thus, cultures of synovial fluid are consistently negative, and blood cultures are positive in <45% of patients. Synovial fluid may be difficult to obtain from inflamed joints and usually contains only 10,000–20,000 leukocytes/μL.

True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients. A single joint such as the hip, knee, ankle, or wrist is usually involved. Synovial fluid, which contains >50,000 leukocytes/μL, can be obtained with ease; the gonococcus is only occasionally evident in gram-stained smears, and cultures of synovial fluid are positive in <40% of cases. Blood cultures are almost always negative.

Because it is difficult to isolate gonococci from synovial fluid and blood, specimens for culture should be obtained from potentially infected mucosal sites. Cultures and gram-stained smears of skin lesions are occasionally positive. All specimens for culture should be plated onto Thayer-Martin agar directly or in special transport media at the bedside and transferred promptly to the microbiology laboratory in an atmosphere of 5% CO_2, as generated in a candle jar. NAA-based assays are extremely sensitive in detecting gonococcal DNA in synovial fluid. A dramatic alleviation of symptoms within 12–24 h after the initiation of appropriate antibiotic therapy supports a clinical diagnosis of the DGI syndrome if cultures are negative.

TREATMENT **Gonococcal Arthritis**

Initial treatment consists of ceftriaxone (1 g IV or IM every 24 h) to cover possible penicillin-resistant organisms. Once local and systemic signs are clearly resolving and if the sensitivity of the isolate permits, the 7-day course of therapy can be completed with an oral agent such as ciprofloxacin (500 mg twice daily). If penicillin-susceptible organisms are isolated, amoxicillin (500 mg three times daily) may be used. Suppurative arthritis usually responds to needle aspiration of involved joints and 7–14 days of antibiotic treatment. Arthroscopic lavage or arthrotomy is rarely required. Patients with DGI should be treated for *Chlamydia trachomatis* infection unless this infection is ruled out by appropriate testing.

It is noteworthy that arthritis symptoms similar to those seen in DGI occur in meningococcemia. A dermatitis-arthritis syndrome, purulent monarthritis, and reactive polyarthritis have been described. All respond to treatment with IV penicillin.

SPIROCHETAL ARTHRITIS

Lyme disease

Lyme disease due to infection with the spirochete *Borrelia burgdorferi* causes arthritis in up to 70% of persons who are not treated. Intermittent arthralgias and myalgias—but not arthritis—occur within days or weeks of inoculation of the spirochete by the *Ixodes* tick. Later, there are three patterns of joint disease: (1) Fifty percent of untreated persons experience intermittent episodes of monarthritis or oligoarthritis involving the knee and/or other large joints. The symptoms wax and wane without treatment over months, and each year 10–20% of patients report loss of joint symptoms. (2) Twenty percent of untreated persons develop a pattern of waxing and waning arthralgias. (3) Ten percent of untreated patients develop chronic inflammatory synovitis that results in erosive lesions and destruction of the joint. Serologic tests for IgG antibodies to *B. burgdorferi* are positive in >90% of persons with Lyme arthritis, and an NAA-based assay detects *Borrelia* DNA in 85%.

TREATMENT **Lyme Arthritis**

Lyme arthritis generally responds well to therapy. A regimen of oral doxycycline (100 mg twice daily for 30 days), oral amoxicillin (500 mg four times daily for 30 days), or parenteral ceftriaxone (2 g/d for 2–4 weeks) is recommended. Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy. Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

Syphilitic arthritis

Articular manifestations occur in different stages of syphilis. In early congenital syphilis, periarticular swelling and immobilization of the involved limbs (Parrot's pseudoparalysis) complicate osteochondritis of long bones. Clutton's joint, a late manifestation of congenital syphilis that typically develops between ages 8 and 15 years, is caused by chronic painless synovitis with effusions of large joints, particularly the knees and elbows. Secondary syphilis may be associated with arthralgias, with symmetric arthritis of the knees and ankles and occasionally of the shoulders and wrists, and with sacroiliitis. The arthritis follows a subacute to chronic course

with a mixed mononuclear and neutrophilic synovial-fluid pleocytosis (typical cell counts, 5000–15,000/μL). Immunologic mechanisms may contribute to the arthritis, and symptoms usually improve rapidly with penicillin therapy. In tertiary syphilis, Charcot's joint results from sensory loss due to tabes dorsalis. Penicillin is not helpful in this setting.

MYCOBACTERIAL ARTHRITIS

Tuberculous arthritis accounts for ~1% of all cases of tuberculosis and 10% of extrapulmonary cases. The most common presentation is chronic granulomatous monarthritis. An unusual syndrome, Poncet's disease, is a reactive symmetric form of polyarthritis that affects persons with visceral or disseminated tuberculosis. No mycobacteria are found in the joints, and symptoms resolve with antituberculous therapy.

Unlike tuberculous osteomyelitis, which typically involves the thoracic and lumbar spine (50% of cases), tuberculous arthritis primarily involves the large weight-bearing joints, in particular the hips, knees, and ankles, and only occasionally involves smaller non-weight-bearing joints. Progressive monarticular swelling and pain develop over months or years, and systemic symptoms are seen in only half of all cases. Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts. Coexistent active pulmonary tuberculosis is unusual.

Aspiration of the involved joint yields fluid with an average cell count of 20,000/μL, with ~50% neutrophils. Acid-fast staining of the fluid yields positive results in fewer than one-third of cases, and cultures are positive in 80%. Culture of synovial tissue taken at biopsy is positive in ~90% of cases and shows granulomatous inflammation in most. NAA methods can shorten the time to diagnosis to 1 or 2 days. Radiographs reveal peripheral erosions at the points of synovial attachment, periarticular osteopenia, and eventually joint-space narrowing. Therapy for tuberculous arthritis is the same as that for tuberculous pulmonary disease, requiring the administration of multiple agents for 6–9 months. Therapy is more prolonged in immunosuppressed individuals such as those infected with HIV.

Various atypical mycobacteria found in water and soil may cause chronic indolent arthritis. Such disease results from trauma and direct inoculation associated with farming, gardening, or aquatic activities. Smaller joints, such as the digits, wrists, and knees, are usually involved. Involvement of tendon sheaths and bursae is typical. The mycobacterial species involved include *Mycobacterium marinum*, *M. avium-intracellulare*, *M. terrae*, *M. kansasii*, *M. fortuitum*, and *M. chelonae*. In persons who have HIV infection or are receiving immunosuppressive therapy, hematogenous spread to the joints has been reported for *M. kansasii*, *M. avium-intracellulare*, and *M. haemophilum*. Diagnosis usually requires biopsy and culture, and therapy is based on antimicrobial susceptibility patterns.

FUNGAL ARTHRITIS

Fungi are an unusual cause of chronic monarticular arthritis. Granulomatous articular infection with the endemic dimorphic fungi *Coccidioides immitis*, *Blastomyces dermatitidis*, and (less commonly) *Histoplasma capsulatum* **(Fig. 21-2)** results from hematogenous seeding or direct extension from bony lesions in persons with disseminated disease. Joint involvement is an unusual complication of sporotrichosis (infection with *Sporothrix schenckii*) among gardeners and other persons who work with soil or sphagnum moss. Articular sporotrichosis is six times more common among men than among women, and alcoholics and other debilitated hosts are at risk for polyarticular infection.

Candida infection involving a single joint'usually the knee, hip, or shoulder'results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread. *Candida* infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints. Unusual cases of arthritis due to *Aspergillus* species, *Cryptococcus neoformans*, *Pseudallescheria boydii*, and the dematiaceous fungi also have resulted from direct inoculation or disseminated hematogenous infection in immunocompromised persons.

The synovial fluid in fungal arthritis usually contains 10,000–40,000 cells/μL, with ~70% neutrophils. Stained specimens and cultures of synovial tissue often confirm the diagnosis of fungal arthritis when studies of synovial fluid give negative results. Treatment consists of drainage and lavage of the joint and systemic administration of an antifungal agent directed at a specific pathogen. The doses and duration of therapy are the same as for disseminated disease (see Part 8, Section 16). Intraarticular instillation of amphotericin B has been used in addition to IV therapy.

VIRAL ARTHRITIS

Viruses produce arthritis by infecting synovial tissue during systemic infection or by provoking an immunologic reaction that involves joints. As many as 50% of women report persistent arthralgias, and 10% report frank arthritis within 3 days of the rash that follows

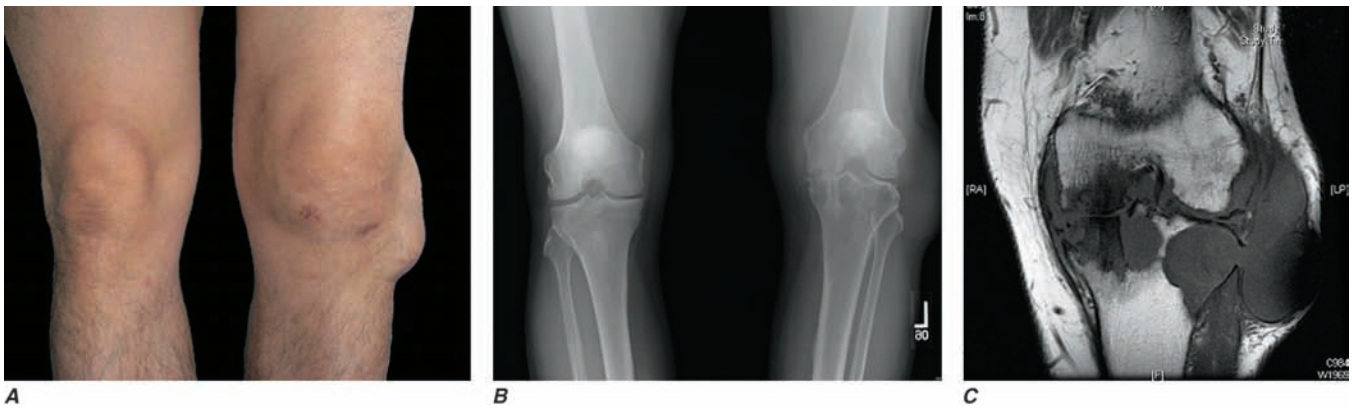


FIGURE 21-2

Chronic arthritis caused by Histoplasma capsulatum in the left knee. ***A.*** A man in his sixties from El Salvador presented with a history of progressive knee pain and difficulty walking for several years. He had undergone arthroscopy for a meniscal tear 7 years before presentation (without relief) and had received several intraarticular glucocorticoid injections. The patient developed significant deformity of the knee over time, including a large effusion in the lateral aspect. ***B.*** An x-ray of the knee showed multiple abnormalities, including severe medial femorotibial joint-space narrowing, several large subchondral cysts within the tibia and the patellofemoral compartment, a large suprapatellar joint effusion, and a large soft tissue mass projecting laterally over the knee. ***C.*** MRI further defined these abnormalities and demonstrated the cystic nature of the lateral knee abnormality. Synovial biopsies demonstrated chronic inflammation with giant cells, and cultures grew *H. capsulatum* after 3 weeks of incubation. All clinical cystic lesions and the effusion resolved after 1 year of treatment with itraconazole. The patient underwent a left total knee replacement for definitive treatment. (*Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.*)

natural infection with rubella virus and within 2–6 weeks after receipt of live-virus vaccine. Episodes of symmetric inflammation of fingers, wrists, and knees uncommonly recur for >1 year, but a syndrome of chronic fatigue, low-grade fever, headaches, and myalgias can persist for months or years. IV immunoglobulin has been helpful in selected cases. Self-limited monarticular or migratory polyarthritis may develop within 2 weeks of the parotitis of mumps; this sequela is more common among men than among women. Approximately 10% of children and 60% of women develop arthritis after infection with parvovirus B19. In adults, arthropathy sometimes occurs without fever or rash. Pain and stiffness, with less prominent swelling (primarily of the hands but also of the knees, wrists, and ankles), usually resolve within weeks, although a small proportion of patients develop chronic arthropathy.

About 2 weeks before the onset of jaundice, up to 10% of persons with acute hepatitis B develop an immune complex–mediated, serum sickness–like reaction with maculopapular rash, urticaria, fever, and arthralgias. Less common developments include symmetric arthritis involving the hands, wrists, elbows, or ankles and morning stiffness that resembles a flare of rheumatoid arthritis. Symptoms resolve at the time jaundice develops. Many persons with chronic hepatitis C infection report persistent arthralgia or arthritis, both in the presence and in the absence of cryoglobulinemia.



Painful arthritis involving larger joints often accompanies the fever and rash of several arthropod-borne viral infections, including those caused by chikungunya, O'nyong-nyong, Ross River, Mayaro, and Barmah Forest viruses. Symmetric arthritis involving the hands and wrists may occur during the convalescent phase of infection with lymphocytic choriomeningitis virus. Patients infected with an enterovirus frequently report arthralgias, and echovirus has been isolated from patients with acute polyarthritis.

Several arthritis syndromes are associated with HIV infection. Reactive arthritis with painful lower-extremity oligoarthritis often follows an episode of urethritis in HIV-infected persons. HIV-associated reactive arthritis appears to be extremely common among persons with the HLA-B27 haplotype, but sacroiliac joint disease is unusual and is seen mostly in the absence of HLA-B27. Up to one-third of HIV-infected persons with psoriasis develop psoriatic arthritis. Painless monarthropathy and persistent symmetric polyarthropathy occasionally complicate HIV infection. Chronic persistent oligoarthritis of the shoulders, wrists, hands, and knees occurs in women infected with human T cell lymphotropic virus type I. Synovial thickening, destruction of articular cartilage, and leukemic-appearing atypical lymphocytes in synovial fluid are characteristic, but progression to T cell leukemia is unusual.

PARASITIC ARTHRITIS



Arthritis due to parasitic infection is rare. The guinea worm *Dracunculus medinensis* may cause destructive joint lesions in the lower extremities as migrating gravid female worms invade joints or cause ulcers in adjacent soft tissues that become secondarily infected. Hydatid cysts infect bones in 1–2% of cases of infection with *Echinococcus granulosus*. The expanding destructive cystic lesions may spread to and destroy adjacent joints, particularly the hip and pelvis. In rare cases, chronic synovitis has been associated with the presence of schistosomal eggs in synovial biopsies. Monarticular arthritis in children with lymphatic filariasis appears to respond to therapy with diethylcarbamazine even in the absence of microfilariae in synovial fluid. Reactive arthritis has been attributed to hookworm, *Strongyloides*, *Cryptosporidium*, and *Giardia* infection in case reports, but confirmation is required.

POSTINFECTIOUS OR REACTIVE ARTHRITIS

Reactive polyarthritis develops several weeks after ~1% of cases of nongonococcal urethritis and 2% of enteric infections, particularly those due to *Yersinia enterocolitica*, *Shigella flexneri*, *Campylobacter jejuni*, and *Salmonella* species. Only a minority of these patients have the other findings of classic reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash. Studies have identified microbial DNA or antigen in synovial fluid or blood, but the pathogenesis of this condition is poorly understood.

Reactive arthritis is most common among young men (except after *Yersinia* infection) and has been linked to the HLA-B27 locus as a potential genetic predisposing factor. Patients report painful, asymmetric oligoarthritis that affects mainly the knees, ankles, and feet. Low-back pain is common, and radiographic evidence of sacroiliitis is found in patients with long-standing disease. Most patients recover within 6 months, but prolonged recurrent disease is more common in cases that follow chlamydial urethritis. Anti-inflammatory agents help relieve symptoms, but the role of prolonged antibiotic therapy in eliminating microbial antigen from the synovium is controversial.

Migratory polyarthritis and fever constitute the usual presentation of acute rheumatic fever in adults (Chap. 7). This presentation is distinct from that of poststreptococcal reactive arthritis, which also follows infections with group A *Streptococcus* but is not migratory, lasts beyond the typical 3-week maximum of acute rheumatic fever, and responds poorly to aspirin.

INFECTIONS IN PROSTHETIC JOINTS

Infection complicates 1–4% of total joint replacements. The majority of infections are acquired intraoperatively or immediately postoperatively as a result of wound breakdown or infection; less commonly, these joint infections develop later after joint replacement and are the result of hematogenous spread or direct inoculation. The presentation may be acute, with fever, pain, and local signs of inflammation, especially in infections due to *S. aureus*, pyogenic streptococci, and enteric bacilli. Alternatively, infection may persist for months or years without causing constitutional symptoms when less virulent organisms, such as coagulase-negative staphylococci or diphtheroids, are involved. Such indolent infections usually are acquired during joint implantation and are discovered during evaluation of chronic unexplained pain or after a radiograph shows loosening of the prosthesis; the erythrocyte sedimentation rate and C-reactive protein level are usually elevated in such cases.

The diagnosis is best made by needle aspiration of the joint; accidental introduction of organisms during aspiration must be avoided meticulously. Synovial fluid pleocytosis with a predominance of polymorphonuclear leukocytes is highly suggestive of infection, since other inflammatory processes uncommonly affect prosthetic joints. Culture and Gram's stain usually yield the responsible pathogen. Sonication of explanted prosthetic material can improve the yield of culture, presumably by breaking up bacterial biofilms on the surfaces of prostheses. Use of special media for unusual pathogens such as fungi, atypical mycobacteria, and *Mycoplasma* may be necessary if routine and anaerobic cultures are negative.

TREATMENT Prosthetic Joint Infections

Treatment includes surgery and high doses of parenteral antibiotics, which are given for 4–6 weeks because bone is usually involved. In most cases, the prosthesis must be replaced to cure the infection. Implantation of a new prosthesis is best delayed for several weeks or months because relapses of infection occur most commonly within this time frame. In some cases, reimplantation is not possible, and the patient must manage without a joint, with a fused joint, or even with amputation. Cure of infection without removal of the prosthesis is occasionally possible in cases that are due to streptococci or pneumococci and that lack radiologic evidence of loosening of the prosthesis. In these cases, antibiotic therapy must be initiated within several days of the onset of infection, and the joint should be

drained vigorously by open arthrotomy or arthroscopically. In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, suppression of the infection with antibiotics may be a reasonable goal. A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and ciprofloxacin is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration. This approach, which is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase, requires confirmation in prospective trials.

Prevention

To avoid the disastrous consequences of infection, candidates for joint replacement should be selected with care. Rates of infection are particularly high among patients with rheumatoid arthritis, persons who have undergone previous surgery on the joint, and persons with medical conditions requiring immunosuppressive therapy. Perioperative antibiotic prophylaxis, usually with cefazolin, and measures to decrease intraoperative contamination, such as laminar flow, have lowered the rates of perioperative infection to <1% in many centers. After implantation, measures should be taken to prevent or rapidly treat extraarticular infections that might give rise to hematogenous spread to the prosthesis. The effectiveness of prophylactic antibiotics for the prevention of hematogenous infection after dental procedures has not been demonstrated; in fact, viridans streptococci and other components of the oral flora are extremely unusual causes of prosthetic joint infection. Accordingly, the American Dental Association and the American Academy of Orthopaedic Surgeons do not recommend antibiotic prophylaxis for most dental patients with total joint replacements. They do, however, recommend prophylaxis for patients who may be at high risk of hematogenous infection, including those with inflammatory arthropathies, immunosuppression, type 1 diabetes mellitus, joint replacement within the preceding 2 years, previous prosthetic joint infection, malnourishment, or hemophilia. The recommended regimen is amoxicillin (2 g PO) 1 h before dental procedures associated with a high incidence of bacteremia. Clindamycin (600 mg PO) is suggested for patients allergic to penicillin.

ACKNOWLEDGMENTS

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CHAPTER 22

FIBROMYALGIA

Leslie J. Crofford

DEFINITION

Fibromyalgia (FM) is characterized by chronic widespread musculoskeletal pain and tenderness. Although it is defined primarily as a pain syndrome, FM patients also commonly complain of associated neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. Patients with FM have an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes. Available evidence implicates the central nervous system as key to maintaining pain and other core symptoms of FM and related conditions. The presence of FM is associated with substantial negative consequences for physical and social functioning.

EPIDEMIOLOGY

FM is far more common in women than in men, with a ratio of about 9:1. In population-based studies worldwide, there is general agreement that the prevalence rate is approximately 2–3%, with rates of closer to 5–10% in primary care practices. The prevalence data are similar across socioeconomic classes. Cultural factors may play a role in determining whether patients with FM symptoms seek medical attention; however, even in cultures in which secondary gain is not expected to play a significant role, the prevalence of FM remains in this range.

CLINICAL MANIFESTATIONS

Pain and tenderness

The most common presenting complaint of a patient with FM is "pain all over." Patients with FM have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to FM is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity. Pain should have been present most of the day on most days for at least 3 months.

The clinical pain of FM is associated with increased evoked pain sensitivity. In clinical practice, this is determined by a tender point examination in which the examiner uses the thumbnail to exert pressure of approximately 4 kg/m^2, or the pressure leading to blanching of the tip of the thumbnail, on well-defined musculotendinous sites **(Fig. 22-1)**. American College of Rheumatology classification criteria previously required that 11 of 18 sites be perceived as painful for a diagnosis of FM. In practice, tenderness is a continuous variable, and strict application of a categorical threshold for diagnosis specifics is no longer necessary. Increased pain sensitivity can be demonstrated not only for the mechanical pressure-induced pain used in the clinic but also for nonmuscular mechanical pressure, heat, cold, and other sensory stimuli; this reinforces the idea that the pathogenic mechanisms of FM are not related to specific musculoskeletal pathology but to altered pain processing. New criteria eliminate tender points and focus on clinical symptoms of widespread pain and neuropsychological symptoms.

Patients with FM often have peripheral pain generators that are thought to serve as triggers for the more widespread pain attributed to central nervous system factors. Potential pain generators such as arthritis, bursitis, tendinitis, neuropathies, and other inflammatory or degenerative conditions should be identified by history and physical examination. More subtle pain generators may include joint hypermobility and scoliosis. Patients also may have chronic myalgias triggered by infectious, metabolic, or psychiatric conditions that can serve as

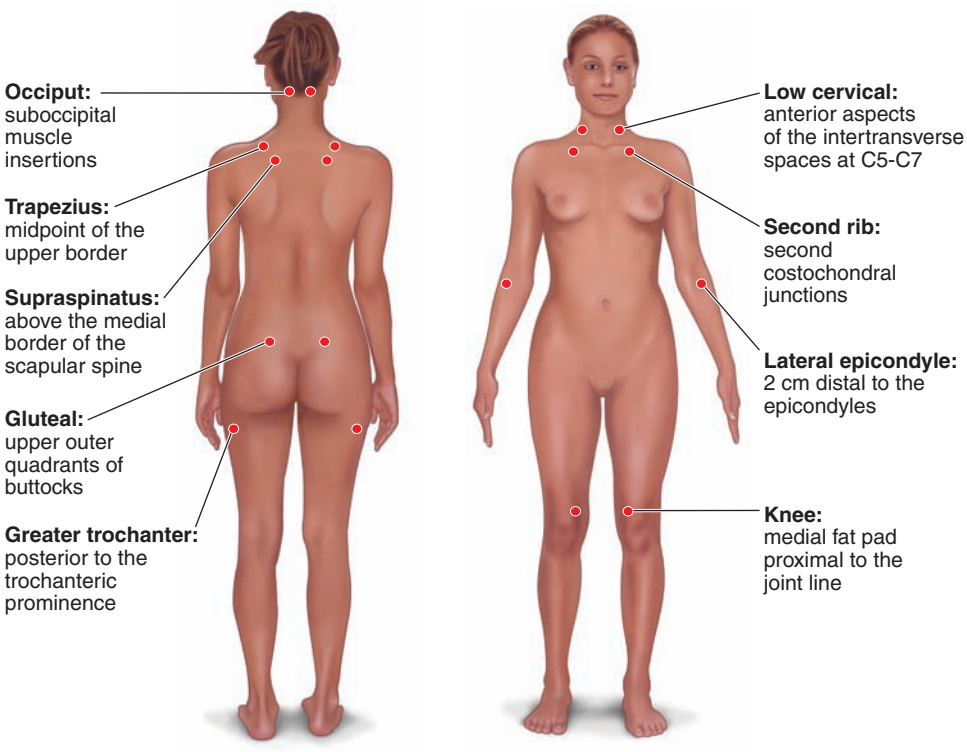


FIGURE 22-1
Tender point assessment in patients with fibromyalgia.

triggers for the development of FM. These conditions are often in the differential diagnosis of patients with FM, and a major challenge is to distinguish the ongoing activity of a triggering condition from FM as a consequence of a comorbid condition that should itself be treated.

Neuropsychological symptoms

In addition to widespread pain, FM patients typically complain of fatigue, stiffness, sleep disturbance, cognitive dysfunction, anxiety, and depression. These symptoms are present to varying degrees in most FM patients but are not present in every patient or at all times. Such symptoms may, however, have an equal or even greater impact on function and quality of life. Fatigue is highly prevalent in patients under primary care who ultimately are diagnosed with FM. Pain, stiffness, and fatigue often are worsened by exercise or unaccustomed activity (postexertional malaise). The sleep complaints include difficulty falling asleep, difficulty staying asleep, and early-morning awakening. Regardless of the specific complaint, patients awake feeling unrefreshed. Patients with FM may meet criteria for restless legs syndrome and sleep-disordered breathing; frank sleep apnea can also be present. Cognitive complaints are characterized as slowness in processing, difficulties with attention or concentration, problems with word retrieval, and short-term memory loss. Studies have demonstrated altered cognitive function in these domains in patients with FM, though speed of processing is age-appropriate. Symptoms of anxiety and depression are common, and the lifetime prevalence of mood disorders in patients with FM approaches 80%. Although depression is neither necessary nor sufficient for the diagnosis of FM, it is important to screen for major depressive disorders by querying for depressed mood and anhedonia. Analysis of genetic factors that are likely to predispose to FM reveals shared neurobiologic pathways with mood disorders, providing the basis for comorbidity.

Overlapping syndromes

Because FM can overlap in presentation with other chronic pain conditions, review of systems often reveals headaches, facial/jaw pain, regional myofascial pain particularly involving the neck or back, and arthritis. Visceral pain complaints involving the gastrointestinal tract, bladder, and pelvic or perineal region are also often present. Patients may or may not meet defined criteria for specific syndromes. It is important for patients to understand that there may be shared pathways that mediate symptoms and that using treatment strategies effective for one condition may help with global symptom management.

Comorbid conditions

FM is often comorbid with chronic musculoskeletal, infectious, metabolic, or psychiatric conditions. Whereas FM is present in only 2–5% of the general population, it occurs in 20% or more of patients with degenerative or inflammatory rheumatic disorders, probably because these conditions serve as peripheral pain generators to alter central pain-processing pathways. Similarly, chronic infectious, metabolic, or psychiatric diseases associated with musculoskeletal pain can mimic FM and/or serve as a trigger for the development of FM. It is particularly important for clinicians to be sensitive to pain management of these comorbid conditions so that when FM emerges, as characterized by pain outside the boundaries of what could reasonably be explained by the triggering condition, development of neuropsychological symptoms, or tenderness on physical examination, treatment of central pain processes will be undertaken rather than continuing to focus on treating peripheral or inflammatory causes of pain.

Psychosocial considerations

Symptoms of FM often have their onset and are exacerbated during periods of high levels of real or perceived stress. This may reflect an interaction between central stress physiology, vigilance or anxiety, and central pain-processing pathways. Understanding current psychosocial stressors will aid in patient management as many factors that exacerbate symptoms cannot be addressed by using pharmacologic approaches. Furthermore, there is a high prevalence of exposure to previous interpersonal and other forms of violence in patients with FM and related conditions. If posttraumatic stress disorder is an issue, the clinician should be aware of it and consider treatment options.

Functional impairment

It is crucial to evaluate the impact of FM symptoms on function and role fulfillment. In defining the success of a management strategy, improved function is a key measure. Functional assessment should include physical, mental, and social domains. Understanding where role functioning falls short will assist in establishing treatment goals.

DIFFERENTIAL DIAGNOSIS

Because musculoskeletal pain is such a common complaint, the differential diagnosis of FM is broad. Table 22-1 lists some of the more common conditions that should be considered. Patients with inflammatory causes for widespread pain should be identifiable on the basis of specific history, physical findings, and laboratory or radiographic tests.

TABLE 22-1

COMMON CONDITIONS IN THE DIFFERENTIAL DIAGNOSIS OF FIBROMYALGIA

Inflammatory
Polymyalgia rheumatica
Inflammatory arthritis: rheumatoid arthritis, spondyloarthritides
Connective tissues diseases: systemic lupus erythematosus, Sjögren's syndrome
Infectious
Hepatitis C
Human immunodeficiency virus (HIV)
Lyme disease
Parvovirus B19
Epstein-Barr virus
Noninflammatory
Degenerative joint/spine/disk disease
Myofascial pain syndromes
Bursitis, tendinitis, repetitive strain injuries
Endocrine
Hypo- or hyperthyroidism
Hyperparathyroidism
Neurologic diseases
Multiple sclerosis
Neuropathic pain syndromes
Psychiatric disease
Major depressive disorder
Drugs
Statins
Aromatase inhibitors

LABORATORY OR RADIOGRAPHIC TESTING

Routine laboratory and radiographic tests are normal in patients with FM, and so diagnostic testing is focused on excluding other diagnoses and evaluating for pain generators or comorbid conditions (Table 22-2). Most

TABLE 22-2

LABORATORY AND RADIOGRAPHIC TESTING IN PATIENTS WITH FIBROMYALGIA SYMPTOMS

Routine
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
Complete blood count (CBC)
Complete metabolic panel
Thyroid-stimulating hormone (TSH)
Guided by history and physical examination
Antinuclear antibody (ANA)
Anti-SSA (anti-Sjögren's syndrome A) and anti-SSB
Rheumatoid factor and anticyclic citrullinated peptide (anti-CCP)
Creatine phosphokinase (CPK)
Viral and bacterial serologies
Spine and joint radiographs

patients with a new complaint of chronic widespread pain should be assessed for the most common entities in the differential diagnosis. Radiographic testing should be used sparingly and only for diagnosis of inflammatory arthritis. After the patient has been evaluated thoroughly, repeat testing is discouraged unless the symptom complex changes. Particularly to be discouraged is advanced imaging (MRI) of the spine unless there are features suggesting inflammatory spine disease or neurologic symptoms.

GENETICS AND PHYSIOLOGY

As in most complex diseases, it is likely that a number of genes contribute to vulnerability to the development of FM. To date, these genes appear to be in pathways controlling pain sensitivity and stress response. Some of the genetic underpinnings of FM are shared across other chronic pain conditions. For example, catechol-O-methyltransferase, which controls the synaptic levels of norepinephrine and dopamine, has been associated with pain sensitivity in the general population and certain polymorphisms or haplotypes have been associated with FM, chronic fatigue syndrome, and temporomandibular disorder. Polymorphisms of the β-adrenergic receptor and dopamine receptor are also associated with FM and other chronic pain conditions. Genes associated with metabolism, transport, and receptors of serotonin and other monoamines have also been implicated in FM and overlapping conditions. Taken together, the pathways in which polymorphisms have been identified in FM patients further implicate central factors as mediating the physiology that leads to FM clinical manifestations.

Psychophysical testing of patients with FM has demonstrated altered sensory afferent pain processing and impaired descending noxious inhibitory control leading to hyperalgesia and allodynia. Functional MRI and other research imaging procedures clearly demonstrate activation of the brain regions involved in the experience of pain in response to stimuli that are innocuous in study participants without FM. Pain perception in FM patients is influenced by the emotional and cognitive dimensions, such as catastrophizing and perceptions of control, providing a solid basis for recommendations for cognitive and behavioral treatment strategies.

APPROACH TO THE PATIENT Fibromyalgia

FM occurs commonly and has an extraordinary impact on functioning and health-related quality of life; however, symptoms and impact can be managed effectively by physicians and other health professionals. Developing a partnership with patients with a goal of understanding and implementing a treatment strategy and choosing appropriate nonpharmacologic and pharmacologic treatments are essential for improving the outcome of FM.

TREATMENT Fibromyalgia

NONPHARMACOLOGIC TREATMENT Patients with chronic pain, fatigue, and other neuropsychological symptoms require a framework for understanding the symptoms that have such an important impact on their function and quality of life. Providing explanation of the genetics, triggers, and physiology of FM can be an important adjunct in relieving the associated anxiety as well as reducing the overall cost of health care resources. In addition, patients must be educated regarding the expectations for treatment. The physician should focus on improved function and quality of life rather than elimination of pain. Illness behaviors should be discouraged, and behaviors that focus on improved function strongly encouraged.

Treatment strategies should include physical conditioning, with encouragement to begin at low levels of aerobic exercise with slow but consistent advancement. Patients who have been physically inactive or who report postexertional malaise may do best in supervised or water-based programs to start. Treatments that incorporate improved physical function with relaxation, such as yoga and Tai Chi, may also be helpful. Strength training may be recommended after a patient has reached his or her aerobic goals. Exercise programs are helpful for reductions in tenderness and for enhanced self-efficacy. Cognitive-behavioral strategies to improve sleep hygiene and reduce illness behaviors can also be helpful in management.

PHARMACOLOGIC APPROACHES It is essential for the clinician to treat any comorbid triggering condition and clearly delineate for the patient the treatment goals for each medication. For example, glucocorticoids or nonsteroidal anti-inflammatory drugs may be useful for management of inflammatory triggers but are not effective for FM-related symptoms. At present, the treatment approaches that have proved most successful in FM patients target afferent or descending pain pathways. Table 22-3 outlines the drugs with demonstrated effectiveness. It should be emphasized strongly that opioid analgesics are to be avoided in patients with FM. These agents have no demonstrated efficacy in FM and are associated with opioid-induced hyperalgesia that can worsen both symptoms and function. Utilization of single agents to treat multiple symptom domains is

TABLE 22-3

PHARMACOLOGIC AGENTS EFFECTIVE FOR TREATMENT OF FIBROMYALGIA
Antidepressants: balanced serotonin:norepinephrine reuptake inhibition
Amitryptiline
Duloxetine[a]
Milnacipran[a]
Anticonvulsants: ligands of the alpha-2-delta subunit of voltage-gated calcium channels
Gabapentin
Pregabalin[a]

[a]Approved for fibromyalgia by the U.S. Food and Drug Administration.

strongly encouraged. For example, if a patient's symptom complex is dominated by pain and sleep disturbance, using an agent that exerts both analgesic and sleep-promoting effects is desirable. These agents include sedating antidepressants such as amitriptyline or alpha-2-delta ligands such as gabapentin and pregabalin. For patients with pain associated with fatigue, anxiety, or depression, drugs that have both analgesic and antidepressant/anxiolytic effects, such as duloxetine or milnacipran, may be the best first choice.

CHAPTER 23

ARTHRITIS ASSOCIATED WITH SYSTEMIC DISEASE, AND OTHER ARTHRITIDES

Carol A. Langford ■ Brian F. Mandell

ARTHRITIS ASSOCIATED WITH SYSTEMIC DISEASE

ARTHROPATHY OF ACROMEGALY

Acromegaly is the result of excessive production of growth hormone by an adenoma in the anterior pituitary gland. The excessive secretion of growth hormone along with insulin-like growth factor I stimulates proliferation of cartilage, periarticular connective tissue, and bone, resulting in several musculoskeletal problems, including osteoarthritis, back pain, muscle weakness, and carpal tunnel syndrome.

Osteoarthritis is a common feature, most often affecting the knees, shoulders, hips, and hands. Single or multiple joints may be affected. Hypertrophy of cartilage initially produces radiographic widening of the joint space. The newly synthesized cartilage is abnormally susceptible to fissuring, ulceration, and destruction. Ligamental laxity of joints further contributes to the development of osteoarthritis. Cartilage degrades, the joint space narrows, and subchondral sclerosis and osteophytes develop. Joint examination reveals crepitus and laxity. Joint fluid is noninflammatory. Calcium pyrophosphate dihydrate crystals are found in the cartilage in some cases of acromegaly arthropathy and, when shed into the joint, these can elicit attacks of pseudogout. Chondrocalcinosis may be observed on radiographs. Back pain is extremely common, perhaps as a result of spine hypermobility. Spine radiographs show normal or widened intervertebral disk spaces, hypertrophic anterior osteophytes, and ligamental calcification. These changes are similar to those observed in patients with diffuse idiopathic skeletal hyperostosis. Dorsal kyphosis in conjunction with elongation of the ribs contributes to the development of the barrel chest seen in acromegalic patients. The hands and feet become enlarged, owing to soft tissue proliferation. The fingers are thickened and have spadelike distal tufts. One-third of patients have a thickened heel pad. Approximately 25% of patients have Raynaud's phenomenon. Carpal tunnel syndrome occurs in about half of patients. The median nerve is compressed by excess connective tissue in the carpal tunnel. Patients with acromegaly could develop proximal muscle weakness, which is thought to be caused by the effect of growth hormone on muscle. Serum muscle enzyme levels and electromyography are normal. Muscle biopsy specimens show muscle fibers of varying size but with no inflammation.

ARTHROPATHY OF HEMOCHROMATOSIS

Hemochromatosis is a disorder of iron storage. Excessive amounts of iron are absorbed from the intestine, leading to iron deposition in parenchymal cells, which results in impairment of organ function. Symptoms of hemochromatosis usually begin between the ages of 40 and 60, but can occur earlier. Arthropathy, which occurs in 20–40% of patients, usually begins after the age of 50 and may be the first clinical feature of hemochromatosis. The arthropathy is an osteoarthritis-like disorder affecting the small joints of the hands, followed later by larger joints such as knees, ankles, shoulders, and hips. The second and third metacarpophalangeal joints of both hands are often the first and prominent joints affected; this may provide an important clue to the possibility of hemochromatosis because these joints are not predominantly affected by "routine" osteoarthritis. Patients experience some morning stiffness and pain with use of involved joints. The affected joints are enlarged and mildly tender. Radiographs show narrowing of the joint space, subchondral sclerosis, subchondral cysts, and juxtaarticular proliferation of bone with frequent hooklike osteophytes.

The synovial fluid is noninflammatory. The synovium shows mild to moderate proliferation of iron containing lining cells, fibrosis, and some mononuclear cell infiltration. In approximately half of patients, there is evidence of calcium pyrophosphate deposition disease (CPPD), and some patients experience episodes of acute pseudogout.

Iron may damage the articular cartilage in several ways. Iron catalyzes superoxide-dependent lipid peroxidation, which may play a role in joint damage. In animal models, ferric iron has been shown to interfere with collagen formation and increase the release of lysosomal enzymes from cells in the synovial membrane. Iron inhibits synovial tissue pyrophosphatase in vitro and, therefore, may inhibit pyrophosphatase in vivo, resulting in chondrocalcinosis.

TREATMENT **Arthropathy of Hemochromatosis**

The treatment of hemochromatosis is repeated phlebotomy. Unfortunately, this treatment has little effect on established arthritis, which, along with chondrocalcinosis, may progress. Symptomatic treatment of the arthritis consists of administration of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as tolerated. Acute pseudogout attacks are treated with high doses of an NSAID or a short course of glucocorticoids. Hip or knee total joint replacement has been successful in advanced disease.

HEMOPHILIC ARTHROPATHY

Hemophilia is a sex-linked recessive genetic disorder characterized by the absence or deficiency of factor VIII (hemophilia A, or classic hemophilia) or factor IX (hemophilia B, or Christmas disease). Hemophilia A constitutes 85% of cases. Spontaneous hemarthrosis is a common problem with both types of hemophilia and can lead to a deforming arthritis. The frequency and severity of hemarthrosis are related to the degree of clotting factor deficiency. Hemarthrosis is not common in other disorders of coagulation such as von Willebrand disease, factor V deficiency, warfarin therapy, or thrombocytopenia.

Hemarthrosis occurs after one year of age, when the child begins to walk and run. In order of frequency, the joints most commonly affected are the knees, ankles, elbows, shoulders, and hips. Small joints of the hands and feet are occasionally involved.

In the initial stage of arthropathy, hemarthrosis produces a warm, tensely swollen, and painful joint. The patient holds the affected joint in flexion and guards against any movement. Blood in the joint remains liquid because of the absence of intrinsic clotting factors and the absence of tissue thromboplastin in the synovium. The synovial blood is resorbed over a period of a week or longer, depending on the size of the hemarthrosis. Joint function usually returns to normal or baseline in about two weeks. Low-grade temperature elevation may accompany hemarthrosis, but a fever >101 warrants concern for infection.

Recurrent hemarthrosis may result in chronic arthritis. The involved joints remain swollen, and flexion deformities develop. Joint motion may be restricted and function severely limited. Restricted joint motion, or laxity with subluxation, are features of end-stage disease.

Bleeding into muscle and soft tissue also causes musculoskeletal dysfunction. When bleeding into the iliopsoas muscle occurs, the hip is held in flexion because of the pain, resulting in a hip flexion contracture. Rotation of the hip is preserved, which distinguishes this problem from hemarthrosis or other causes of hip synovitis. Expansion of the hematoma may place pressure on the femoral nerve, resulting in a femoral neuropathy. Hemorrhage into a closed compartment space, such as the calf or volar compartment in the forearm, can result in muscle necrosis, neuropathy, and flexion deformities of the ankles, wrists, and fingers. When bleeding involves periosteum or bone, a painful pseudotumor forms. These occur distal to the elbows or knees in children and improve with treatment of the hemophilia. Surgical removal is indicated if the pseudotumor continues to enlarge. In adults, pseudotumors occur in the femur and pelvis and are usually refractory to treatment. When bleeding occurs in muscle, cysts may develop within the muscle. Needle aspiration of a cyst is contraindicated because it can induce further bleeding; however, if they become secondarily infected, drainage may be necessary (after factor repletion).

Septic arthritis rarely occurs in hemophilia and is difficult to distinguish from acute hemarthrosis on physical examination. If there is serious suspicion of an infected joint, the joint should be aspirated immediately, the fluid cultured, and the patient started on antibiotics that provide broad coverage, including *staphylococcus*, until the results of the culture return. Clotting-factor deficiency should be corrected before arthrocentesis to minimize the risk of traumatic bleeding.

Radiographs of joints reflect the stage of disease. In early stages, there is only capsule distention; later, juxtaarticular osteopenia, marginal erosions, and subchondral cysts develop. Late in the disease, the joint space is narrowed and there is bony overgrowth similar to osteoarthritis.

TREATMENT **Hemarthrosis**

The treatment of musculoskeletal bleeding is initiated with the immediate infusion of factor VIII or IX at the first sign of joint or muscle hemorrhage. Patients who

have developed factor inhibitors are at greater risk for joint damage and may benefit from receiving recombinant activated factor VII or activated prothrombin complex concentrate. The joint should be rested in a position of forced extension, as tolerated, to avoid contracture. Analgesia should be provided; ideally, the nonselective NSAIDs, which can diminish platelet function, should be avoided if possible. Selective cyclooxygenase-2 inhibitors do not interfere with platelet function and may be preferable based upon a demonstrated increased risk of upper GI bleeding and theoretical risk of increased articular bleeding with nonselective NSAIDs. Synovectomy, open or arthroscopic, may be attempted in patients with chronic symptomatic synovial proliferation and recurrent hemarthrosis, although hypertrophied synovium is very vascular and subject to bleeding. Both types of synovectomy reduce the number of hemarthroses. Open surgical synovectomy, however, is associated with some loss of range of motion. Both require aggressive prophylaxis against bleeding. Radiosynovectomy with either yttrium 90 silicate or phosphorus 31 colloid has been effective and may be attempted when surgical synovectomy is not practical. Total joint replacement is indicated for severe joint destruction and incapacitating pain.

ARTHROPATHIES ASSOCIATED WITH HEMOGLOBINOPATHIES

Sickle cell disease

Sickle cell disease is associated with several musculoskeletal abnormalities (Table 23-1). Children under the age of five may develop diffuse swelling, tenderness, and warmth of the hands and feet lasting from one to three weeks. The condition, referred to as *sickle cell dactylitis* or *hand-foot syndrome*, has also been observed in sickle cell thalassemia. Dactylitis is believed to result from infarction of the bone marrow and cortical bone leading to periostitis and soft tissue swelling. Radiographs show periosteal elevation, subperiosteal new bone formation, and areas of radiolucency and increased density involving the metacarpals, metatarsals, and proximal phalanges. These bone changes disappear after several months. The syndrome leaves little or no residual damage. Because hematopoiesis ceases in the small bones of hands and feet with age, the syndrome is rarely seen after age five.

TABLE 23-1

MUSCULOSKELETAL ABNORMALITIES IN SICKLE CELL DISEASE

SICKLE CELL DACTYLITIS	AVASCULAR NECROSIS
Joint effusions in sickle cell crises	Bone changes secondary to marrow hyperplasia
Osteomyelitis	Septic arthritis
Infarction of bone	Gouty arthritis
Infarction of bone marrow	

Sickle cell crisis is associated with periarticular pain and occasionally with joint effusions. The joint and periarticular area are warm and tender. Knees and elbows are most often affected, but other joints can be involved. Joint effusions are usually noninflammatory. Acute synovial infarction can cause a sterile effusion with high synovial fluid neutrophil counts. Synovial biopsies have shown mild lining cell proliferation and microvascular thrombosis with infarctions. Scintigraphic studies have shown decreased marrow uptake adjacent to the involved joint. The treatment is that for sickle cell crisis.

Patients with sickle cell disease seem predisposed to osteomyelitis, which commonly involves the long tubular bones and *Salmonella* is a particularly frequent cause. Radiographs of the involved site show periosteal elevation initially, followed by disruption of the cortex. Treatment of the infection results in healing of the bone lesion. Sickle cell disease is also more frequently associated with bone infarction resulting from vasoocclusion secondary to the sickling of red cells. Bone infarction also occurs in hemoglobin sickle cell disease and sickle cell thalassemia. The bone pain in sickle cell crisis is due to bone and bone marrow infarction. In children, infarction of the epiphyseal growth plate interferes with normal growth of the affected extremity. Radiographically, infarction of the bone cortex results in periosteal elevation and irregular thickening of the bone cortex. Infarction in the bone marrow leads to lysis, fibrosis, and new bone formation. Clinical distinction between osteomyelitis and bone infarctions can be difficult; imaging can be helpful.

Avascular necrosis of the head of the femur occurs in ~5% of patients. It also occurs in the humeral head and less commonly in the distal femur, tibial condyles, distal radius, vertebral bodies, and other juxtaarticular sites. Irregularity of the femoral head and other articular surfaces often results in degenerative joint disease. Radiograph of the affected joint may show patchy radiolucency and density followed by flattening of the bone. MRI is a sensitive technique for detecting early avascular necrosis as well as bone infarction elsewhere. Total hip replacement and placement of prostheses in other joints may improve function and relieve the joint pain in these patients.

Septic arthritis is occasionally encountered in sickle cell disease (Chap. 21). Multiple joints may be infected. Joint infection may result from bacteremia due to splenic dysfunction or fromcontiguous osteomyelitis. The more common microorganisms include *Staphylococcus aureus*, *Streptococcus*, and *Salmonella*. Salmonella does not cause septic arthritis as frequently as osteomyelitis. Acute gouty arthritis is uncommon in sickle cell disease,

even though 40% of patients are hyperuricemic. However, it may occur in patients generally not expected to get gout (younger, including female patients). Hyperuricemia is due to overproduction of uric acid secondary to increased red cell turnover as well as suboptimal renal excretion. Attacks may be polyarticular, and arthrocentesis should be performed as the diagnostic test to distinguish infection from gout or synovial infarction.

The bone marrow hyperplasia in sickle cell disease results in widening of the medullary cavities, thinning of the cortices, and coarse trabeculations and central cupping of the vertebral bodies. These changes are also seen to a lesser degree in hemoglobin sickle cell disease and sickle cell thalassemia. In normal individuals, red marrow is located mostly in the axial skeletal, but in sickle cell disease, red marrow is found in the bones of the extremities and even in the tarsal and carpal bones. Vertebral compression may lead to dorsal kyphosis, and softening of the bone in the acetabulum may result in protrusio acetabuli.

Thalassemia

β Thalassemia is a congenital disorder of hemoglobin synthesis characterized by impaired production of β chains. Bone and joint abnormalities occur in β thalassemia, being most common in the major and intermedia groups. In one study, ~50% of patients with β thalassemia had evidence of symmetric ankle arthropathy, characterized by a dull aching pain aggravated by weight bearing. The onset was most often in the second or third decade of life. The degree of ankle pain in these patients varied. Some patients experienced self-limited ankle pain, which occurred only after strenuous physical activity and lasted several days to weeks. Other patients had chronic ankle pain, which became worse with walking. Symptoms eventually abated in a few patients. Compression of the ankle, calcaneus, or forefoot was painful in some patients. Synovial fluid from two patients was noninflammatory. Radiographs of ankle showed osteopenia, widened medullary spaces, thin cortices, and coarse trabeculations. These findings are largely the result of bone marrow expansion. The joint space was preserved. Specimens of bone from three patients revealed osteomalacia, osteopenia, and microfractures. Increased osteoblasts as well as increased foci of bone resorption were present on the bone surface. Iron staining was found in the bone trabeculae, in osteoid, and in the cement line. Synovium showed hyperplasia of lining cells, which contained deposits of hemosiderin. This arthropathy was considered to be related to the underlying bone pathology. The role of iron overload or abnormal bone metabolism in the pathogenesis of this arthropathy is not known. The arthropathy was treated with analgesics and splints. Patients were also transfused to decrease hematopoiesis and bone marrow expansion.

Patients with β-thalassemia major and intermedia also have involvement of other joints, including the knees, hips, and shoulders. Acquired hemochromatosis with arthropathy has been described in a patient with thalassemia. Gouty arthritis and septic arthritis can occur. Avascular necrosis is not a feature of thalassemia because there is no sickling of red cells leading to thrombosis and infarction.

β-Thalassemia minor (trait) is also associated with joint manifestations. Chronic seronegative oligoarthritis affecting predominantly ankles, wrists, and elbows has been described. These patients had mild persistent synovitis without large effusions. Joint erosions were not seen. Recurrent episodes of an acute asymmetric arthritis have also been reported; episodes last less than a week and may affect knees, ankles, shoulders, elbows, wrists, and metacarpal phalangeal joints. The mechanism for this arthropathy is unknown. Treatment with nonsteroidal drugs was not particularly effective.

MUSCULOSKELETAL DISORDERS ASSOCIATED WITH HYPERLIPIDEMIA

Musculoskeletal or cutaneous manifestations may be the first clinical indication of a specific hereditary disorder of lipoprotein metabolism. Patients with familial hypercholesterolemia (previously referred to as *type II hyperlipoproteinemia*) may have recurrent migratory polyarthritis involving knees and other large peripheral joints and, to a lesser degree, peripheral small joints. Pain ranges from moderate to incapacitating. The involved joints can be warm, erythematous, swollen, and tender. Arthritis usually has a sudden onset, lasts from a few days to two weeks, and does not cause joint damage. Episodes may suggest acute gout attacks. Several attacks occur per year. Synovial fluid from involved joints is not inflammatory and contains few white cells and no crystals. Joint involvement may actually represent inflammatory periarthritis or peritendinitis and not true arthritis. The recurrent, transient nature of the arthritis may suggest rheumatic fever, especially because patients with hyperlipoproteinemia may have an elevated erythrocyte sedimentation rate and elevated antistreptolysin O titers, because the latter are quite common. Attacks of tendinitis, including the large Achilles and patellar tendons, may come on gradually and last only a few days or be acute as described earlier. Patients may be asymptomatic between attacks. Achilles tendinitis and other joint manifestations often precede the appearance of xanthomas and may be the first clinical indication of hyperlipoproteinemia. Attacks of tendinitis may occur following treatment with a lipid-lowering drug. Patients, over time, may develop tendinous xanthomas in the Achilles, patellar, and extensor tendons of the hands and feet. Xanthomas have also been reported in the peroneal

tendon, the plantar aponeurosis, and the periosteum overlying the distal tibia. These xanthomas are located within tendon fibers. Tuberous xanthomas are soft subcutaneous masses located over the extensor surfaces of the elbows, knees, and hands, as well as on the buttocks. They appear in childhood in homozygous patients and, after the age of 30, in heterozygous patients. Patients with elevated plasma levels of very low density lipoprotein (VLDL) and triglyceride (previously referred to as *type IV hyperlipoproteinemia*) may also have a mild inflammatory arthritis affecting large and small peripheral joints, usually in an asymmetric pattern, with only a few joints involved at a time. The onset of arthritis is usually in middle age. Arthritis may be persistent or recurrent, with episodes lasting a few days to weeks. Joint pain is severe in some patients. Patients may experience morning stiffness. Joint tenderness and periarticular hyperesthesia may also be present, as may synovial thickening. Joint fluid is usually noninflammatory and without crystals, but may have increased white blood cell counts with predominantly mononuclear cells. Radiographs may show juxtaarticular osteopenia and cystic lesions. Large bone cysts have been noted in a few patients. Xanthoma and bone cysts are also observed in other lipoprotein disorders. The pathogenesis of arthritis in patients with familial hypercholesterolemia or with elevated levels of VLDL and triglyceride is not well understood. NSAIDs or analgesics usually provide adequate relief of symptoms when used on an as-needed basis.

Clinical improvement may occur in patients as they are treated with lipid-lowering agents; however, patients treated with an HMG-CoA reductase inhibitor may experience myalgias, and a few patients may develop a myopathy, myositis, or even rhabdomyolysis. Patients who develop myositis while on statin therapy may be susceptible to this side effect due to an underlying muscle disorder and should be reevaluated after discontinuation of the drug. Myositis has also been reported with the use of niacin (Chap. 17) but is less common than myalgias.

Musculoskeletal syndromes have not clearly been associated with the more common mixed hyperlipidemias seen in general practice.

OTHER ARTHRITIDES

NEUROPATHIC JOINT DISEASE

Neuropathic joint disease (Charcot's joint) is a progressive destructive arthritis associated with loss of pain sensation, proprioception, or both. Normal muscular reflexes that modulate joint movement are decreased. Without these protective mechanisms, joints are subjected to repeated trauma, resulting in progressive cartilage and bone damage. Neuropathic arthropathy was first described by Jean-Martin Charcot in 1868 in patients with tabes dorsalis. The term *Charcot joint* is commonly used interchangeably with *neuropathic joint*. Today, diabetes mellitus is the most frequent cause of neuropathic joint disease **(Fig. 23-1)**. A variety of other disorders are associated with neuropathic arthritis including leprosy, yaws, syringomyelia, meningomyelocele, congenital indifference to pain, peroneal muscular atrophy (Charcot-Marie-Tooth disease), and amyloidosis. An arthritis resembling neuropathic joint disease has been reported in patients who have received frequent intraarticular glucocorticoid injections into a weight-bearing joint, but this is a rare complication. The distribution of joint involvement depends on the underlying neurologic disorder **(Table 23-2)**. In tabes dorsalis, knees, hips, and ankles are most commonly affected; in syringomyelia, the glenohumeral joint, elbow, and wrist; and in diabetes mellitus, the tarsal and tarsometatarsal joints are most commonly affected.



FIGURE 23-1
Charcot arthropathy associated with diabetes mellitus. Lateral foot radiograph demonstrating complete loss of the arch due to bony fragmentation and dislocation in the midfoot. (*Courtesy of Andrew Neckers, MD and Jean Schils, MD; with permission.*)

Pathology and pathophysiology

The pathologic changes in the neuropathic joint are similar to those found in the severe osteoarthritic joint. There is fragmentation and eventual loss of articular

TABLE 23-2

DISORDERS ASSOCIATED WITH NEUROPATHIC JOINT DISEASE	
Diabetes mellitus	Amyloidosis
Tabes dorsalis	Leprosy
Meningomyelocele	Congenital indifference to pain
Syringomyelia	Peroneal muscular atrophy

cartilage with eburnation of the underlying bone. Osteophytes are found at the joint margins. With more advanced disease, erosions are present on the joint surface. Fractures, devitalized bone, intraarticular loose bodies, and microscopic fragments of cartilage and bone may be present.

At least two underlying mechanisms are believed to be involved in the pathogenesis of neuropathic arthritis. An abnormal autonomic nervous system is thought to be responsible for the dysregulated blood flow to the joint with subsequent resorption of bone. Loss of bone, particularly in the diabetic foot, may be the initial finding. With the loss of deep pain, proprioception, and protective neuromuscular reflexes, the joint is subjected to repeated microtrauma, resulting in ligamental tears and bone fractures. The mechanism of injury that occurs following frequent intraarticular glucocorticoid injections is thought to be due to the analgesic effect of glucocorticoids leading to overuse of an already damaged joint, which results in accelerated cartilage damage, although steroid-induced cartilage damage be more common in some animal species than in humans. It is not understood why only a few patients with neuropathy develop clinically evident neuropathic arthritis.

Clinical manifestations

Neuropathic joint disease usually begins in a single joint and then becomes apparent in other joints, depending on the underlying neurologic disorder. The involved joint progressively becomes enlarged due to bony overgrowth and synovial effusion. Loose bodies may be palpated in the joint cavity. Joint instability, subluxation, and crepitus occur as the disease progresses. Neuropathic joints may develop rapidly, and a totally disorganized joint with multiple bony fragments may evolve in a patient within weeks or months. The amount of pain experienced by the patient is less than would be anticipated based on the degree of joint damage. Patients may experience sudden joint pain from intraarticular fractures of osteophytes or condyles.

Neuropathic arthritis is encountered most often in patients with diabetes mellitus, with the incidence estimated in the range of 0.5%. The usual age of onset is ≥50 years, following several years of diabetes, but exceptions occur. The tarsal and tarsometatarsal joints are most often affected, followed by the metatarsophalangeal and talotibial joints. The knees and spine are occasionally involved. Patients often attribute the onset of foot pain to antecedent trauma such as twisting their foot. Neuropathic changes may develop rapidly following a foot fracture or dislocation. Swelling of the foot and ankle are often present. Downward collapse of the tarsal bones leads to convexity of the sole, referred to as a "rocker foot." Large osteophytes may protrude from the top of the foot. Calluses frequently form over the metatarsal heads and may lead to infected ulcers and osteomyelitis. The value of protective inserts and orthotics, as well as regular foot examination, cannot be overstated. Radiographs may show resorption and tapering of the distal metatarsal bones. The term *Lisfranc fracture-dislocation* is sometimes used to describe the destructive changes at the tarsometatarsal joints.

Diagnosis

The diagnosis of neuropathic arthritis is based on the clinical features and characteristic radiographic findings in a patient with an underlying sensory neuropathy. The differential diagnosis of neuropathic arthritis depends upon the severity of the process and includes osteomyelitis, osteonecrosis, advanced osteoarthritis, stress fractures, and CPPD. Radiographs in neuropathic arthritis initially show changes of osteoarthritis with joint space narrowing, subchondral bone sclerosis, osteophytes, and joint effusions followed later by marked destructive and hypertrophic changes. The radiographic findings of neuropathic arthritis may be difficult to differentiate from those of osteomyelitis, especially in the diabetic foot. The joint margins in a neuropathic joint tend to be distinct, while in osteomyelitis, they are blurred. Imaging studies may be helpful, but cultures of tissue from the joint are often required to exclude osteomyelitis. MRI and bone scans using indium 111–labeled white blood cells or indium 111–labeled immunoglobulin G, which will show an increased uptake in osteomyelitis but not in a neuropathic joint may be useful. A technetium bone scan will not distinguish osteomyelitis from neuropathic arthritis, as increased uptake is observed in both. The joint fluid in neuropathic arthritis is noninflammatory; may be xanthochromic or even bloody; and may contain fragments of synovium, cartilage, and bone. The finding of calcium pyrophosphate dihydrate crystals supports the diagnosis of crystal-associated arthropathy. In the absence of such crystals, an increased number of leukocytes may indicate osteomyelitis.

TREATMENT **Neuropathic Joint Disease**

The primary focus of treatment is to stabilize the joint. Treatment of the underlying disorder, even if successful, does not usually affect established joint disease. Braces and splints are helpful. Their use requires close surveillance, because patients may be unable to appreciate pressure from a poorly adjusted brace. In the diabetic patient, early recognition and treatment of a Charcot's foot by prohibiting weight bearing of the foot for

at least eight weeks may possibly prevent severe disease from developing. Fusion of an unstable joint may improve function and reduce pain, but nonunion is frequent, especially when immobilization of the joint is inadequate.

HYPERTROPHIC OSTEOARTHROPATHY AND CLUBBING

Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of digits and, in more advanced stages, by periosteal new bone formation and synovial effusions. HOA may be primary or familial and begin in childhood. Secondary HOA is associated with intrathoracic malignancies, suppurative and some hypoxemic lung diseases, congenital heart disease, and a variety of other disorders. Clubbing is almost always a feature of HOA but can occur as an isolated manifestation **(Fig. 23-2)**. The presence of clubbing in isolation may be congenital or represent either an early stage or one element in the spectrum of HOA. The presence of isolated acquired clubbing has the same clinical significance as clubbing associated with periostitis.

Pathology and pathophysiology of acquired HOA

In HOA, the bone changes in the distal extremities begin as periostitis followed by new bone formation. At this stage, a radiolucent area may be observed between the new periosteal bone and subjacent cortex. As the process progresses, multiple layers of new bone are deposited, which become contiguous with the cortex and result in cortical thickening. The outer portion of bone is laminated in appearance, with an irregular surface. Initially, the process of periosteal new bone formation involves the proximal and distal diaphyses of the tibia, fibula, radius, and ulna and, less frequently, the femur, humerus, metacarpals, metatarsals, and phalanges. Occasionally, scapulae, clavicles, ribs, and pelvic bones are also affected. The adjacent interosseous membranes may become ossified. The distribution of the bone manifestations is usually bilateral and symmetric. The soft tissue overlying the distal third of the arms and legs may be thickened. Proliferation of connective tissue occurs in the nail bed and volar pad of digits, giving the distal phalanges a clubbed appearance. Small blood vessels in the clubbed digits are dilated and have thickened walls. In addition, the number of arteriovenous anastomoses is increased.



FIGURE 23-2
Clubbing of fingers. (*Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, Copyright 1991, 1995. Used by permission of the American College of Rheumatology.*)

Several theories have been suggested for the pathogenesis of HOA, but many have been disproved or have not explained the development in all clinical disorders associated with HOA. Previously proposed neurogenic and humoral theories are no longer considered likely explanations for HOA. Recent studies have suggested a role for platelets in the development of HOA. It has been observed that megakaryocytes and large platelet particles, present in venous circulation, were fragmented in their passage through normal lung. In patients with cyanotic congenital heart disease and in other disorders associated with right-to-left shunts, these large platelet particles bypass the lung and reach the distal extremities, where they can interact with endothelial cells. Platelet-endothelial activation in the distal portion of extremities may result in the release of platelet-derived growth factor (PDGF) and other factors leading to the proliferation of connective tissue and periosteum. Stimulation of fibroblasts by PDGF and transforming growth factor β results in cell growth and collagen synthesis. Elevated plasma levels of von Willebrand factor antigen have been found in patients with both primary and secondary forms of HOA, indicating endothelial activation or damage. Abnormalities of collagen synthesis have been demonstrated in the involved skin of patients with primary HOA. Other factors are undoubtedly involved in the pathogenesis of HOA, and further studies are needed to better understand this disorder.

Clinical manifestations

Primary or familial HOA, also referred to as *pachydermoperiostitis* or *Touraine-Solente-Golé syndrome*, usually begins insidiously at puberty. In a smaller number of patients, the onset is in the first year of life. The disorder is inherited as an autosomal dominant trait with variable expression and is nine times more common in boys than in girls. Approximately one-third of patients have a family history of primary HOA.

Primary HOA is characterized by clubbing, periostitis, and unusual skin features. A small number of

patients with this syndrome do not express clubbing. The skin changes and periostitis are prominent features of this syndrome. The skin becomes thickened and coarse. Deep nasolabial folds develop, and the forehead may become furrowed. Patients may have heavy-appearing eyelids and ptosis. The skin is often greasy, and there may be excessive sweating of the hands and feet. Patients may also experience acne vulgaris, seborrhea, and folliculitis. In a few patients, the skin over the scalp becomes very thick and corrugated, a feature that has been descriptively termed *cutis verticis gyrata*. The distal extremities, particularly the legs, become thickened owing to proliferation of new bone and soft tissue; when the process is extensive, the distal lower extremities resemble those of an elephant. The periostitis is usually not painful, because it may be in secondary HOA. Clubbing of the fingers may be extensive, producing large, bulbous deformities and clumsiness. Clubbing also affects the toes. Patients may experience articular and periarticular pain, especially in the ankles and knees, and joint motion may be mildly restricted owing to periarticular bone overgrowth. Noninflammatory effusions occur in the wrists, knees, and ankles. Synovial hypertrophy is not found. Associated abnormalities observed in patients with primary HOA include hypertrophic gastropathy, bone marrow failure, female escutcheon, gynecomastia, and cranial suture defects. In patients with primary HOA, the symptoms disappear when adulthood is reached.

HOA secondary to an underlying disease occurs more frequently than primary HOA. It accompanies a variety of disorders and may precede clinical features of the associated disorder by months. Clubbing is more frequent than the full syndrome of HOA in patients with associated illnesses. Because clubbing evolves over months and is usually asymptomatic, it is often recognized first by the physician and not the patient. Patients may experience a burning sensation in their fingertips. Clubbing is characterized by widening of the fingertips, enlargement of the distal volar pad, convexity of the nail contour, and the loss of the normal 15° angle between the proximal nail and cuticle. The thickness of the digit at the base of the nail is greater than the thickness at the distal interphalangeal joint. An objective measurement of finger clubbing can be made by determining the diameter at the base of the nail and at the distal interphalangeal joint of all 10 digits. Clubbing is present when the sum of the individual digit ratios is >10. At the bedside, clubbing can be appreciated by having the patient place the dorsal surface of the distal phalanges of the fourth fingers together with the nails of the fourth fingers opposing each other. Normally, an open area is visible between the bases of the opposing fingernails; when clubbing is present, this open space is no longer visible. The base of the nail feels spongy when compressed, and the nail can be easily rocked on its bed. When clubbing is advanced, the finger may have a drumstick appearance, and the distal interphalangeal joint can be hyperextended. Periosteal involvement in the distal extremities may produce a burning or deep-seated aching pain. The pain can be quite incapacitating and is aggravated by dependency and relieved by elevation of the affected limbs. Pressure applied over the distal forearms and legs or gentle percussion of the distal long bones like the tibia may be quite painful.

Patients may experience joint pain, most often in the ankles, wrists, and knees. Joint effusions may be present; usually, they are small and noninflammatory. The small joints of the hands are rarely affected. Severe joint or long bone pain may be the presenting symptom of an underlying lung malignancy and may precede the appearance of clubbing. In addition, the progression of HOA tends to be more rapid when associated with malignancies, most notably bronchogenic carcinoma. Noninflammatory but variably painful knee effusions may occur prior to the appearance of clubbing and symptoms of distal periostitis. Unlike primary HOA, excessive sweating and oiliness of the skin and thickening of the facial skin are uncommon in secondary HOA.

HOA occurs in 5–10% of patients with intrathoracic malignancies, the most common being bronchogenic carcinoma and pleural tumors **(Table 23-3)**. Lung metastases infrequently cause HOA. HOA is also seen in patients with intrathoracic infections, including lung abscesses, empyema, bronchiectasis, and chronic obstructive lung disease, but uncommonly in pulmonary tuberculosis. HOA may also accompany chronic interstitial pneumonitis, sarcoidosis, and cystic fibrosis. In the latter, clubbing is more common than the full

TABLE 23-3

DISORDERS ASSOCIATED WITH HYPERTROPHIC OSTEOARTHROPATHY

Pulmonary	Cardiovascular
Bronchogenic carcinoma and other neoplasms	Cyanotic congenital heart disease
Lung abscesses, empyema, bronchiectasis	Subacute bacterial endocarditisInfected arterial grafts[a]
Chronic interstitial pneumonitis	Aortic aneurysm[b]
Cystic fibrosis	Aneurysm of major extremity artery[a]
Chronic obstructive lung disease	Patent ductus arteriosus[b]
Sarcoidosis	Arteriovenous fistula of major extremity vessel[a]
Gastrointestinal	Thyroid (thyroid acropachy)
Inflammatory bowel disease	Hyperthyroidism (Graves' disease)
Sprue	
Neoplasms: esophagus, liver, bowel	

[a]Unilateral involvement.
[b]Bilateral lower extremity involvement.

syndrome of HOA. Other causes of clubbing include congenital heart disease with right-to-left shunts, bacterial endocarditis, Crohn's disease, ulcerative colitis, sprue, and neoplasms of the esophagus, liver, and small and large bowel. In patients with congenital heart disease with right-to-left shunts, clubbing alone occurs more often than the full syndrome of HOA.

Unilateral clubbing has been found in association with aneurysms of major extremity arteries, with infected arterial grafts, and with arteriovenous fistulas of brachial vessels. Clubbing of the toes but not fingers has been associated with an infected abdominal aortic aneurysm and patent ductus arteriosus. Clubbing of a single digit may follow trauma and has been reported in tophaceous gout and sarcoidosis. While clubbing occurs more commonly than the full syndrome in most diseases, periostitis in the absence of clubbing has been observed in the affected limb of patients with infected arterial grafts.

Hyperthyroidism (Graves' disease), treated or untreated, is occasionally associated with clubbing and periostitis of the bones of the hands and feet. This condition is referred to as *thyroid acropachy*. Periostitis may be asymptomatic and occurs in the midshaft and diaphyseal portion of the metacarpal and phalangeal bones. Significant hand joint pain may occur; this may respond to successful therapy of the thyroid dysfunction. The long bones of the extremities are seldom affected. Elevated levels of long-acting thyroid stimulator are found in the serum of these patients.

Laboratory findings

The laboratory abnormalities reflect the underlying disorder. The synovial fluid of involved joints has <500 white cells per microliter, and the cells are predominantly mononuclear. Radiographs show a faint radiolucent line beneath the new periosteal bone along the shaft of long bones at their distal end. These changes are observed most frequently at the ankles, wrists, and knees. The ends of the distal phalanges may show osseous resorption. Radionuclide studies show pericortical linear uptake along the cortical margins of long bones that may be present before any radiographic changes.

TREATMENT **Hypertrophic Osteoarthropathy**

The treatment of HOA is to identify the associated disorder and treat it appropriately. The symptoms and signs of HOA may disappear completely with removal or effective chemotherapy of a tumor or with antibiotic therapy and drainage of a chronic pulmonary infection. Vagotomy or percutaneous block of the vagus nerve leads to symptomatic relief in some patients. NSAIDs or analgesics may help control symptoms of HOA.

REFLEX SYMPATHETIC DYSTROPHY SYNDROME

The reflex sympathetic dystrophy syndrome is now referred to as *complex regional pain syndrome, type 1*, by the new Classification of the International Association for the Study of Pain. It is characterized by pain and swelling, usually of a distal extremity, accompanied by vasomotor instability, trophic skin changes, and the rapid development of bony demineralization.

TIETZE SYNDROME AND COSTOCHONDRITIS

Tietze syndrome is manifested by painful swelling of one or more costochondral articulations. The age of onset is usually before 40, and both sexes are affected equally. In most patients, only one joint is involved, usually the second or third costochondral joint. The onset of anterior chest pain may be sudden or gradual. The pain may radiate to the arms or shoulders and is aggravated by sneezing, coughing, deep inspirations, or twisting motions of the chest. The term *costochondritis* is often used interchangeably with *Tietze syndrome*, but some workers restrict the former term to pain of the costochondral articulations without swelling. Costochondritis is observed in patients over age 40; tends to affect the third, fourth, and fifth costochondral joints; and occurs more often in women. Both syndromes may mimic cardiac or upper abdominal causes of pain. Rheumatoid arthritis, ankylosing spondylitis, and reactive arthritis may involve costochondral joints but are distinguished easily by their other clinical features. Other skeletal causes of anterior chest wall pain are xiphoidalgia and the slipping rib syndrome, which usually involves the tenth rib. Malignancies such as breast cancer, prostate cancer, plasma cell cytoma, and sarcoma can invade the ribs, thoracic spine, or chest wall and produce symptoms suggesting Tietze syndrome. Patients with osteomalacia may have significant rib pain, with or without documented micro fractures. These conditions should be distinguishable by radiographs, bone scanning, vitamin D measurement, or biopsy. Analgesics, anti-inflammatory drugs, and local glucocorticoid injections usually relieve symptoms of costochondritis/Tietze syndrome. Care should be taken to avoid overdiagnosing these syndromes in patients with acute chest pain syndromes; many patients will be tender to overly vigorous palpation of the costochondral joints.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome is characterized by multiple areas of localized musculoskeletal pain and tenderness

in association with tender points. The pain is deep and aching and may be accompanied by a burning sensation. Myofascial pain may be regional and follow trauma, overuse, or prolonged static contraction of a muscle or muscle group, which may occur when reading or writing at a desk or working at a computer. In addition, this syndrome may be associated with underlying osteoarthritis of the neck or low back. Pain may be referred from tender points to defined areas distant from the area of original tenderness. Palpation of the tender point reproduces or accentuates the pain. The tender points are usually located in the center of a muscle belly, but they can occur at other sites such as costosternal junctions, the xiphoid process, ligamentous and tendinous insertions, fascia, and fatty areas. Tender point sites in muscle have been described as feeling indurated and taut, and palpation may cause the muscle to twitch. These findings, however, have been shown not to be unique for myofascial pain syndrome, because in a controlled study, they were also present in some "normal" subjects. Myofascial pain most often involves the posterior neck, low back, shoulders, and chest. Chronic pain in the muscles of the posterior neck may involve referral of pain from a tender point in the erector neck muscle or upper trapezius to the head, leading to persistent headaches, which may last for days. Tender points in the paraspinal muscles of the low back may refer pain to the buttock. Pain may be referred down the leg from a tender point in the gluteus medius and can mimic sciatica. A tender point in the infraspinatus muscle may produce local and referred pain over the lateral deltoid and down the outside of the arm into the hand. Injection of a local anesthetic such as 1% lidocaine into the tender point site often results in at least transient pain relief. Another useful technique is first to spray from the tender point toward the area of referred pain with an agent such as ethyl chloride and then to stretch the muscle. This maneuver may need to be repeated several times. Massage and application of ultrasound to the affected area also may be beneficial. Patients should be instructed in methods to prevent muscle stresses related to work and recreation. Posture and resting positions are important in preventing muscle tension. The prognosis in most patients is good. In some patients, regionally localized myofascial pain syndrome may seem to evolve into more generalized fibromyalgia (Chap. 22). Abnormal or nonrestorative sleep is a common accompaniment in these patients and may need to be specifically addressed.

NEOPLASIAS AND ARTHRITIS

Primary tumors and tumor-like disorders of synovium are uncommon, but should be considered in the differential diagnosis of monarticular joint disease. In addition, metastases to bone and primary bone tumors adjacent to a joint may produce joint symptoms.

Pigmented villonodular synovitis (PVNS) is characterized by the slowly progressive, exuberant, benign proliferation of synovial tissue, usually involving a single joint. The most common age of onset is in the third decade, and women are affected slightly more often than men. The cause of this disorder is unknown.

The synovium has a brownish color and numerous large, finger-like villi that fuse to form pedunculated nodules. There is marked hyperplasia of synovial cells in the stroma of the villi. Hemosiderin granules and lipids are found in the cytoplasm of macrophages and in the interstitial tissue. Multinucleated giant cells may be present. The proliferative synovium grows into the subsynovial tissue and invades adjacent cartilage and bone.

The clinical picture of pigmented villonodular synovitis is characterized by the insidious onset of persistent swelling and pain in affected joints, most commonly the knee. Other joints affected include the hips, ankles, calcaneocuboid joints, elbows, and small joints of the fingers or toes. The disease may also involve the common flexor sheath of the hands or fingers. Less commonly, tendon sheaths in the wrist, ankle, or foot may be involved. Symptoms of pain, a catching sensation, or stiffness may initially be mild and intermittent and may be present for years before the patient seeks medical attention. Radiographs may show joint space narrowing, erosions, and subchondral cysts. The joint fluid contains blood and is dark red or almost black in color. Lipid-containing macrophages may be present in the fluid. The joint fluid may be clear if hemorrhage has not occurred. Some patients have polyarticular involvement.

The treatment of pigmented villonodular synovitis is complete synovectomy. With incomplete synovectomy, the villonodular synovitis recurs, and the rate of tissue growth may be faster than it was originally. Irradiation of the involved joint has been successful in some patients.

Synovial chondromatosis is a disorder characterized by multiple focal metaplastic growths of normal-appearing cartilage in the synovium or tendon sheath. Segments of cartilage break loose and continue to grow as loose bodies. When calcification and ossification of loose bodies occur, the disorder is referred to as *synovial osteochondromatosis*. The disorder is usually monarticular and affects young to middle-aged individuals. The knee is most often involved, followed by hip, elbow, and shoulder. Symptoms are pain, swelling, and decreased motion of the joint. Radiographs may show several rounded calcifications within the joint cavity. Treatment is synovectomy; however, as in PVNS, the tumor may recur.

Synovial sarcoma is a malignant neoplasm often found near a large joint of both upper and lower extremities, being more common in the lower extremity. It seldom arises within the joint itself. Synovial sarcomas constitute 10% of soft tissue sarcomas. The tumor is believed

to arise from primitive mesenchymal tissue that differentiates into epithelial cells and/or spindle cells. Small foci of calcification may be present in the tumor mass. It occurs most often in young adults and is more common in men. The tumor presents as a slowly growing deep-seated mass near a joint, without much pain. The area of the knee is the most common site, followed by the foot, ankle, elbow, and shoulder. Other primary sites include the buttocks, abdominal wall, retroperitoneum, and mediastinum. The tumor spreads along tissue planes. The most common site of visceral metastasis is lung. The diagnosis is made by biopsy. Treatment is wide resection of the tumor, including adjacent muscle and regional lymph nodes, followed by chemotherapy and radiation therapy. Amputation of the involved distal extremity may be required. Chemotherapy may be beneficial in some patients with metastatic disease. Isolated pulmonary metastasis can be surgically removed. The five-year survival rate with treatment is variable depending on the staging of the tumor, ranging from approximately 25% to 60% or higher. Synovial sarcomas tend to recur locally and metastasize to regional lymph nodes, lungs, and skeleton.

In addition to the rare direct metastases of solid cell tumors to the highly vascular synovium, neoplasia arising from nonarticular organ sites can affect joints in other ways. Acute leukemias in children can mimic juvenile inflammatory arthritis with severe joint pain and fever. In adults, chronic and acute myeloid leukemia can rarely infiltrate the synovium. The rarely occurring hairy cell leukemia has a peculiar tendency to cause episodic inflammatory oligoarthritis and tenosynovitis; these episodes are dramatic and mimic acute gout attacks. They respond to potent anti-inflammatory therapy with glucocorticoids; with remission of the leukemia, they may abate. Carcinomas can be associated with several paraneoplastic articular syndromes, including hypertrophic pulmonary osteoarthropathy (discussed earlier). Acute palmar fasciitis with polyarthritis is a well-described, but rare association with certain cancers, mainly adenocarcinomas. Clinically, this is fairly abrupt in onset with pain in the MCP and PIP joints of the hands with rapidly evolving contractures of the fingers due to thickening of the palmar (flexor) tendons. A similar syndrome can be seen in diabetics. Paraneoplastic arthritis has been described and may occur in several patterns: asymmetric predominantly lower extremity joints and symmetric, polyarthritis with hand joint involvement. Tumors were often found after the onset of the arthritis, although many patients had a preceding period of malaise or weight loss. The onset is often acute, and patients tend to be older males. These features should raise the specter of an underlying malignancy (or viral infection such as hepatitis C) as the cause of the arthritis. In one series, the symptoms resolved with successful therapy of the malignancy but did not recur with relapse of the malignancy. Dermatomyositis is also well described as a paraneoplastic syndrome and may have joint pain and arthritis as components of the syndrome. Malignancy associated arthritis may be responsive to NSAID therapy and to treatment of the primary neoplasm.

Acknowledgment

This chapter represents a revised version of the chapter authored by Dr. Bruce C. Gilliland that was in the previous editions of Harrison's Principles of Internal Medicine. Dr. Gilliland passed away on February 17, 2007, and had been a contributor to Harrison's since the 11th edition.

CHAPTER 24

PERIARTICULAR DISORDERS OF THE EXTREMITIES

Carol A. Langford ■ Bruce C. Gilliland[a]

A number of periarticular disorders have become increasingly common over the past two to three decades, due in part to greater participation in recreational sports by individuals of a wide range of ages. Periarticular disorders most commonly affect the knee or shoulder. With the exception of bursitis, hip pain is most often articular or is being referred from disease affecting another structure (Chap. 18). This chapter discusses some of the more common periarticular disorders.

BURSITIS

Bursitis is inflammation of a bursa, which is a thin-walled sac lined with synovial tissue. The function of the bursa is to facilitate movement of tendons and muscles over bony prominences. Excessive frictional forces from overuse, trauma, systemic disease (e.g., rheumatoid arthritis, gout), or infection may cause bursitis. *Subacromial bursitis* (subdeltoid bursitis) is the most common form of bursitis. The subacromial bursa, which is contiguous with the subdeltoid bursa, is located between the undersurface of the acromion and the humeral head and is covered by the deltoid muscle. Bursitis is caused by repetitive overhead motion and often accompanies rotator cuff tendinitis. Another frequently encountered form is *trochanteric bursitis*, which involves the bursa around the insertion of the gluteus medius onto the greater trochanter of the femur. Patients experience pain over the lateral aspect of the hip and upper thigh and have tenderness over the posterior aspect of the greater trochanter. External rotation and resisted abduction of the hip elicit pain. *Olecranon bursitis* occurs over the posterior elbow, and when the area is acutely inflamed, infection or gout should be excluded by aspirating the bursa and performing a Gram stain and culture on the fluid as well as examining the fluid for urate crystals. *Achilles bursitis* involves the bursa located above the insertion of the tendon to the calcaneus and results from overuse and wearing tight shoes. *Retrocalcaneal bursitis* involves the bursa that is located between the calcaneus and posterior surface of the Achilles tendon. The pain is experienced at the back of the heel, and swelling appears on the medial and/or lateral side of the tendon. It occurs in association with spondyloarthropathies, rheumatoid arthritis, gout, or trauma. *Ischial bursitis* (weaver's bottom) affects the bursa separating the gluteus medius from the ischial tuberosity and develops from prolonged sitting and pivoting on hard surfaces. *Iliopsoas bursitis* affects the bursa that lies between the iliopsoas muscle and hip joint and is lateral to the femoral vessels. Pain is experienced over this area and is made worse by hip extension and flexion. *Anserine bursitis* is an inflammation of the sartorius bursa located over the medial side of the tibia just below the knee and under the conjoint tendon and is manifested by pain on climbing stairs. Tenderness is present over the insertion of the conjoint tendon of the sartorius, gracilis, and semitendinosus. *Prepatellar bursitis* (housemaid's knee) occurs in the bursa situated between the patella and overlying skin and is caused by kneeling on hard surfaces. Gout or infection may also occur at this site. Treatment of bursitis consists of prevention of the aggravating situation, rest of the involved part, administration of a nonsteroidal anti-inflammatory drug (NSAID) where appropriate for an individual patient, or local glucocorticoid injection.

[a]Deceased. A contributor to *Harrison's Principles of Internal Medicine* since the 11th edition, Dr. Gilliland passed away on February 17, 2007.

ROTATOR CUFF TENDINITIS AND IMPINGEMENT SYNDROME

Tendinitis of the rotator cuff is the major cause of a painful shoulder and is currently thought to be caused by inflammation of the tendon(s). The rotator cuff consists of the tendons of the supraspinatus, infraspinatus, subscapularis, and teres minor muscles, and inserts on the humeral tuberosities. Of the tendons forming the rotator cuff, the supraspinatus tendon is the most often affected, probably because of its repeated impingement (*impingement syndrome*) between the humeral head and the undersurface of the anterior third of the acromion and coracoacromial ligament above as well as the reduction in its blood supply that occurs with abduction of the arm **(Fig. 24-1)**. The tendon of the infraspinatus and that of the long head of the biceps are less commonly involved. The process begins with edema and hemorrhage of the rotator cuff, which evolves to fibrotic thickening and eventually to rotator cuff degeneration with tendon tears and bone spurs. Subacromial bursitis also accompanies this syndrome. Symptoms usually appear after injury or overuse, especially with activities involving elevation of the arm with some degree of forward flexion. Impingement syndrome occurs in persons participating in baseball, tennis, swimming, or occupations that require repeated elevation of the arm. Those over age 40 are particularly susceptible. Patients complain of a dull aching in the shoulder, which may interfere with sleep. Severe pain is experienced when the arm is actively abducted into an overhead position.

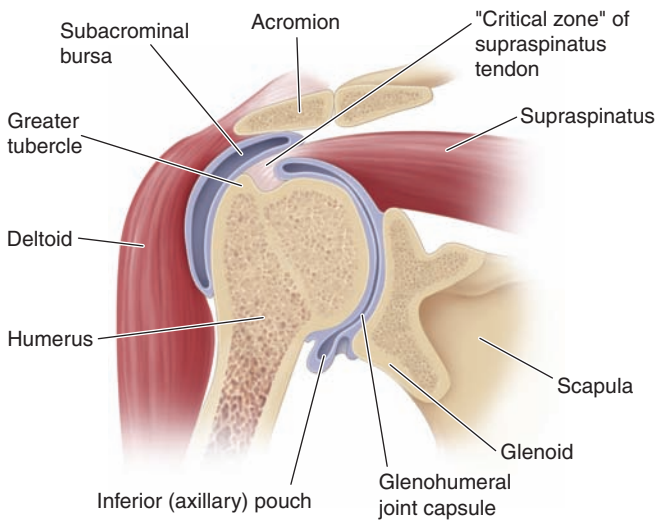


FIGURE 24-1

Coronal section of the shoulder illustrating the relationships of the glenohumeral joint, the joint capsule, the subacromial bursa, and the rotator cuff (supraspinatus tendon). (*From F Kozin, in Arthritis and Allied Conditions, 13th ed, WJ Koopman [ed]. Baltimore, Williams & Wilkins, 1997, with permission.*)

The arc between 60° and 120° is especially painful. Tenderness is present over the lateral aspect of the humeral head just below the acromion. NSAIDs, local glucocorticoid injection, and physical therapy may relieve symptoms. Surgical decompression of the subacromial space may be necessary in patients refractory to conservative treatment.

Patients may tear the supraspinatus tendon acutely by falling on an outstretched arm or lifting a heavy object. Symptoms are pain along with weakness of abduction and external rotation of the shoulder. Atrophy of the supraspinatus muscles develops. The diagnosis is established by arthrogram, ultrasound, or MRI. Surgical repair may be necessary in patients who fail to respond to conservative measures. In patients with moderate-to-severe tears and functional loss, surgery is indicated.

CALCIFIC TENDINITIS

This condition is characterized by deposition of calcium salts, primarily hydroxyapatite, within a tendon. The exact mechanism of calcification is not known but may be initiated by ischemia or degeneration of the tendon. The supraspinatus tendon is most often affected because it is frequently impinged on and has a reduced blood supply when the arm is abducted. The condition usually develops after age 40. Calcification within the tendon may evoke acute inflammation, producing sudden and severe pain in the shoulder. However, it may be asymptomatic or not related to the patient's symptoms.

BICIPITAL TENDINITIS AND RUPTURE

Bicipital tendinitis, or tenosynovitis, is produced by friction on the tendon of the long head of the biceps as it passes through the bicipital groove. When the inflammation is acute, patients experience anterior shoulder pain that radiates down the biceps into the forearm. Abduction and external rotation of the arm are painful and limited. The bicipital groove is very tender to palpation. Pain may be elicited along the course of the tendon by resisting supination of the forearm with the elbow at 90° (Yergason's supination sign). Acute rupture of the tendon may occur with vigorous exercise of the arm and is often painful. In a young patient, it should be repaired surgically. Rupture of the tendon in an older person may be associated with little or no pain and is recognized by the presence of persistent swelling of the biceps ("Popeye" muscle) produced by the retraction of the long head of the biceps. Surgery is usually not necessary in this setting.

DE QUERVAIN'S TENOSYNOVITIS

In this condition, inflammation involves the abductor pollicis longus and the extensor pollicis brevis as these

tendons pass through a fibrous sheath at the radial styloid process. The usual cause is repetitive twisting of the wrist. It may occur in pregnancy, and it also occurs in mothers who hold their babies with the thumb outstretched. Patients experience pain on grasping with their thumb, such as with pinching. Swelling and tenderness are often present over the radial styloid process. The Finkelstein sign is positive, which is elicited by having the patient place the thumb in the palm and close the fingers over it. The wrist is then ulnarly deviated, resulting in pain over the involved tendon sheath in the area of the radial styloid. Treatment consists initially of splinting the wrist and an NSAID. When severe or refractory to conservative treatment, glucocorticoid injections can be very effective.

PATELLAR TENDINITIS (JUMPER'S KNEE)

Tendinitis involves the patellar tendon at its attachment to the lower pole of the patella. Patients may experience pain when jumping during basketball or volleyball, going up stairs, or doing deep knee squats. Tenderness is noted on examination over the lower pole of the patella. Treatment consists of rest, icing, and NSAIDs, followed by strengthening and increasing flexibility.

ILIOTIBIAL BAND SYNDROME

The iliotibial band is a thick connective tissue that runs from the ilium to the fibula. Patients with iliotibial band syndrome most commonly present with aching or burning pain at the site where the band courses over the lateral femoral condyle of the knee; pain may also radiate up the thigh, toward the hip. Predisposing factors for iliotibial band syndrome include a varus alignment of the knee, excessive running distance, poorly fitted shoes, or continuous running on uneven terrain. Treatment consists of rest, NSAIDs, physical therapy, and addressing risk factors such as shoes and running surface. Glucocorticoid injection into the area of tenderness can provide relief, but running must be avoided for at least two weeks after the injection. Surgical release of the iliotibial band has been helpful in rare patients for whom conservative treatment has failed.

ADHESIVE CAPSULITIS

Often referred to as "frozen shoulder," adhesive capsulitis is characterized by pain and restricted movement of the shoulder, usually in the absence of intrinsic shoulder disease. Adhesive capsulitis may follow bursitis or tendinitis of the shoulder or be associated with systemic disorders such as chronic pulmonary disease, myocardial infarction, and diabetes mellitus. Prolonged immobility of the arm contributes to the development of adhesive capsulitis. Pathologically, the capsule of the shoulder is thickened, and a mild chronic inflammatory infiltrate and fibrosis may be present.

Adhesive capsulitis occurs more commonly in women after age 50. Pain and stiffness usually develop gradually but progress rapidly in some patients. Night pain is often present in the affected shoulder and pain may interfere with sleep. The shoulder is tender to palpation, and both active and passive movement are restricted. Radiographs of the shoulder show osteopenia. The diagnosis is typically made by physical examination but can be confirmed if necessary by arthrography, in that only a limited amount of contrast material, usually <15 mL, can be injected under pressure into the shoulder joint.

In most patients, the condition improves spontaneously 1–3 years after onset. While pain usually improves, many patients are left with some limitation of shoulder motion. Early mobilization of the arm following an injury to the shoulder may prevent the development of this disease. Physical therapy provides the foundation of treatment for adhesive capsulitis. Local injections of glucocorticoids and NSAIDs may also provide relief of symptoms. Slow but forceful injection of contrast material into the joint may lyse adhesions and stretch the capsule, resulting in improvement of shoulder motion. Manipulation under anesthesia may be helpful in some patients.

LATERAL EPICONDYLITIS (TENNIS ELBOW)

Lateral epicondylitis, or tennis elbow, is a painful condition involving the soft tissue over the lateral aspect of the elbow. The pain originates at or near the site of attachment of the common extensors to the lateral epicondyle and may radiate into the forearm and dorsum of the wrist. The pain usually appears after work or recreational activities involving repeated motions of wrist extension and supination against resistance. Most patients with this disorder injure themselves in activities other than tennis, such as pulling weeds, carrying suitcases or briefcases, or using a screwdriver. The injury in tennis usually occurs when hitting a backhand with the elbow flexed. Shaking hands and opening doors can reproduce the pain. Striking the lateral elbow against a solid object may also induce pain.

The treatment is usually rest along with administration of an NSAID. Ultrasound, icing, and friction massage may also help relieve pain. When pain is severe, the elbow is placed in a sling or splinted at 90° of flexion. When the pain is acute and well localized, injection of a glucocorticoid using a small-gauge needle may be effective. Following injection, the patient should be advised to rest the arm for at least one month and avoid activities that would aggravate the elbow.

Once symptoms have subsided, the patient should begin rehabilitation to strengthen and increase flexibility of the extensor muscles before resuming physical activity involving the arm. A forearm band placed 2.5–5.0 cm (1–2 in.) below the elbow may help to reduce tension on the extensor muscles at their attachment to the lateral epicondyle. The patient should be advised to restrict activities requiring forcible extension and supination of the wrist. Improvement may take several months. The patient may continue to experience mild pain but, with care, can usually avoid the return of debilitating pain. Occasionally, surgical release of the extensor aponeurosis may be necessary.

MEDIAL EPICONDYLITIS

Medial epicondylitis is an overuse syndrome resulting in pain over the medial side of the elbow with radiation into the forearm. The cause of this syndrome is considered to be repetitive resisted motions of wrist flexion and pronation, which lead to microtears and granulation tissue at the origin of the pronator teres and forearm flexors, particularly the flexor carpi radialis. This overuse syndrome is usually seen in patients >35 years and is much less common than lateral epicondylitis. It occurs most often in work-related repetitive activities, but also occurs with recreational activities such as swinging a golf club (golfer's elbow) or throwing a baseball. On physical examination, there is tenderness just distal to the medial epicondyle over the origin of the forearm flexors. Pain can be reproduced by resisting wrist flexion and pronation with the elbow extended. Radiographs are usually normal. The differential diagnosis of patients with medial elbow symptoms include tears of the pronator teres, acute medial collateral ligament tear, and medial collateral ligament instability. Ulnar neuritis has been found in 25–50% of patients with medial epicondylitis and is associated with tenderness over the ulnar nerve at the elbow as well as hypesthesia and paresthesia on the ulnar side of the hand.

The initial treatment of medial epicondylitis is conservative, involving rest, NSAIDs, friction massage, ultrasound, and icing. Some patients may require splinting. Injections of glucocorticoids at the painful site may also be effective. Patients should be instructed to rest for at least one month. Also, patients should start physical therapy once the pain has subsided. In patients with chronic debilitating medial epicondylitis that remains unresponsive after at least a year of treatment, surgical release of the flexor muscle at its origin may be necessary and is often successful.

PLANTAR FASCIITIS

Plantar fasciitis is a common cause of foot pain in adults, with the peak incidence occurring in people between the ages of 40 and 60 years. It is also seen more frequently in a younger population consisting of runners, aerobic exercise dancers, and ballet dancers. The pain originates at or near the site of the plantar fascia attachment to the medial tuberosity of the calcaneus. Several factors that increase the risk of developing plantar fasciitis include obesity, pes planus (flat foot or absence of the foot arch when standing), pes cavus (high-arched foot), limited dorsiflexion of the ankle, prolonged standing, walking on hard surfaces, and faulty shoes. In runners, excessive running and a change to a harder running surface may precipitate plantar fasciitis.

The diagnosis of plantar fasciitis can usually be made on the basis of history and physical examination alone. Patients experience severe pain with the first steps on arising in the morning or following inactivity during the day. The pain usually lessens with weight-bearing activity during the day, only to worsen with continued activity. Pain is made worse on walking barefoot or up stairs. On examination, maximal tenderness is elicited on palpation over the inferior heel corresponding to the site of attachment of the plantar fascia.

Imaging studies may be indicated when the diagnosis is not clear. Plain radiographs may show heel spurs, which are of little diagnostic significance. Ultrasonography in plantar fasciitis can demonstrate thickening of the fascia and diffuse hypoechogenicity, indicating edema at the attachment of the plantar fascia to the calcaneus. MRI is a sensitive method for detecting plantar fasciitis, but it is usually not required for establishing the diagnosis.

The differential diagnosis of inferior heel pain includes calcaneal stress fractures, the spondyloarthritides, rheumatoid arthritis, gout, neoplastic or infiltrative bone processes, and nerve compression/entrapment syndromes.

Resolution of symptoms occurs within 12 months in more than 80% of patients with plantar fasciitis. The patient is advised to reduce or discontinue activities that can exacerbate plantar fasciitis. Initial treatment consists of ice, heat, massage, and stretching. Stretching of the plantar fascia and calf muscles are commonly employed and can be beneficial. Orthotics provide medial arch support and can be effective. Foot strapping or taping are commonly performed, and some patients may benefit by wearing a night splint designed to keep the ankle in a neutral position. A short course of NSAIDs can be given to patients when the benefits outweigh the risks. Local glucocorticoid injections have also been shown to be efficacious, but may carry an increased risk for plantar fascia rupture. Plantar fasciotomy is reserved for those patients who have failed to improve after at least 6–12 months of conservative treatment.

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APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

Alexander Kratz ■ Michael A. Pesce ■ Robert C. Basner ■ Andrew J. Einstein

This Appendix contains tables of reference values for laboratory tests, special analytes, and special function tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. The reference or "normal" ranges given in this appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be utilized in the interpretation of laboratory data. Values supplied in this Appendix reflect typical reference ranges in adults. Pediatric reference ranges may vary significantly from adult values.

In preparing the Appendix, the authors have taken into account the fact that the system of international units (SI, système international d'unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in "traditional" or conventional units. Therefore, both systems are provided in the Appendix. The dual system is also used in the text except for (1) those instances in which the numbers remain the same but only the terminology is changed (mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given; and (2) most pressure measurements (e.g., blood and cerebrospinal fluid pressures), when the traditional units (mmHg, mmH_2O) are used. In all other instances in the text the SI unit is followed by the traditional unit in parentheses.

REFERENCE VALUES FOR LABORATORY TESTS

TABLE 1

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	Not applicable	Ratio >2.1
ADAMTS13 activity	P	≥0.67	≥67%
ADAMTS13 inhibitor activity	P	Not applicable	≤0.4 U
ADAMTS13 antibody	P	Not applicable	≤18 U
$Alpha_2$ antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
Bone marrow: See Table 7			
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-dimer	P	220–740 ng/mL FEU	220–740 ng/mL FEU
Differential blood count	WB		
Relative counts:			
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Absolute counts:			
Neutrophils		$1.42–6.34 \times 10^9$/L	1420–6340/mm^3
Bands		$0–0.45 \times 10^9$/L	0–450/mm^3
Lymphocytes		$0.71–4.53 \times 10^9$/L	710–4530/mm^3
Monocytes		$0.14–0.72 \times 10^9$/L	140–720/mm^3
Eosinophils		$0–0.54 \times 10^9$/L	0–540/mm^3
Basophils		$0–0.18 \times 10^9$/L	0–180/mm^3
Erythrocyte count	WB		
Adult males		$4.30–5.60 \times 10^{12}$/L	$4.30–5.60 \times 10^6$/mm^3
Adult females		$4.00–5.20 \times 10^{12}$/L	$4.00–5.20 \times 10^6$/mm^3
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Females		0–20 mm/h	0–20 mm/h
Males		0–15 mm/h	0–15 mm/h
Euglobulin lysis time	P	7200–14400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150 %
Factor XIII screen	P	Not applicable	Present
Factor inhibitor assay	P	<0.5 Bethesda Units	<0.5 Bethesda Units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 µg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham's test (acid serum)	WB	Negative	Negative

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Hematocrit	WB		
Adult males		0.388–0.464	38.8–46.4
Adult females		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood:	WB		
Adult males		133–162 g/L	13.3–16.2 g/dL
Adult females		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A_2		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A_2, or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Immature platelet fraction (IPF)	WB	0.011–0.061	1.1–6.1%
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 μkat/L	13–100 μ/L
Count (WBC)	WB	3.54–9.06 × 10^9/L	3.54–9.06 × 10^3/mm^3
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 μm^3
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 μg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	165–415 × 10^9/L	165–415 × 10^3/mm^3
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 μm^3
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	Not applicable	Not present
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Protoporphyrin, free erythrocyte	WB	0.28–0.64 μmol/L of red blood cells	16–36 μg/dL of red blood cells
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Adult males		0.008–0.023 red cells	0.8–2.3% red cells
Adult females		0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Serotonin release assay	S	<0.2 release	<20% release
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Total eosinophils	WB	150–300 × 10^6/L	150–300/mm^3
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
von Willebrand factor (vWF) antigen (factor VIII:R antigen)			
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see “Leukocytes”			

Abbreviations: JF, joint fluid; P, plasma; PRP, platelet-rich plasma; S, serum; WB, whole blood.

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	49–294 μmol/L	0.5–3.0 mg/dL
Adrenocorticotropin (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (ALT, SGPT)	S	0.12–0.70 μkat/L	7–41 U/L
Albumin	S	40–50 g/L	4.0–5.0 mg/dL
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal sodium diet	S, P	<443 pmol/L	<16 ng/dL
Upright, normal	S, P	111–858 pmol/L	4–31 ng/dL
Alpha fetoprotein (adult)	S	0–8.5 μg/L	0–8.5 ng/mL
$Alpha_1$ antitrypsin	S	1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH_3	P	11–35 μmol/L	19–60 μg/dL
Amylase (method dependent)	S	0.34–1.6 μkat/L	20–96 U/L

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Androstendione (adult)	S		
Males		0.81–3.1 nmol/L	23–89 ng/dL
Females			
Premenopausal		0.91–7.5 nmol/L	26–214 ng/dL
Postmenopausal		0.46–2.9 nmol/L	13–82 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 μkat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S		
Male		0.94–1.78 g/L	94–178 mg/dL
Female		1.01–1.99 g/L	101–199 mg/dL
Apolipoprotein B	S		
Male		0.55–1.40 g/L	55–140 mg/dL
Female		0.55–1.25 g/L	55–125 mg/dL
Arterial blood gases	WB		
$[HCO_3^-]$		22–30 mmol/L	22–30 meq/L
P_{CO_2}		4.3–6.0 kPa	32–45 mmHg
pH		7.35–7.45	7.35–7.45
P_{O_2}		9.6–13.8 kPa	72–104 mmHg
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 μkat/L	12–38 U/L
Autoantibodies	S		
Anti-centromere antibody IgG		≤29 AU/mL	≤29 AU/mL
Anti-double-strand (native) DNA		<25 IU/L	<25 IU/L
Anti-glomerular basement membrane antibodies			
Qualitative IgG, IgA		Negative	Negative
Quantitative IgG antibody		≤19 AU/mL	≤19 AU/mL
Anti-histone antibodies		<1.0 U	<1.0 U
Anti-Jo-1 antibody		≤29 AU/mL	≤29 AU/mL
Anti-mitochondrial antibody		Not applicable	<20 Units
Anti-neutrophil cytoplasmic autoantibodies		Not applicable	<1:20
Serine proteinase 3 antibodies		≤19 AU/mL	≤19 AU/mL
Myeloperoxidase antibodies		≤19 AU/mL	≤19 AU/mL
Antinuclear antibody		Not applicable	Negative at 1:40
Anti-parietal cell antibody		Not applicable	None detected
Anti-RNP antibody		Not applicable	<1.0 U
Anti-Scl 70 antibody		Not applicable	<1.0 U
Anti-Smith antibody		Not applicable	<1.0 U
Anti–smooth muscle antibody		Not applicable	<1.0 U
Anti-SSA antibody		Not applicable	<1.0 U
Anti-SSB antibody		Not applicable	Negative
Anti-thyroglobulin antibody		<40 kIU/L	<40 IU/mL
Anti-thyroid peroxidase antibody		<35 kIU/L	<35 IU/mL
B-type natriuretic peptide (BNP)	P	Age and gender specific: <100 ng/L	Age and gender specific: <100 pg/mL
Bence Jones protein, serum qualitative	S	Not applicable	None detected
Bence Jones protein, serum quantitative	S		
Free kappa		3.3–19.4 mg/L	0.33–1.94 mg/dL
Free lambda		5.7–26.3 mg/L	0.57–2.63 mg/dL
K/L ratio		0.26–1.65	0.26–1.65
Beta-2-microglobulin	S	1.1–2.4 mg/L	1.1–2.4 mg/L
Bilirubin	S		
Total		5.1–22 μmol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 μmol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 μmol/L	0.2–0.9 mg/dL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C peptide	S	0.27–1.19 nmol/L	0.8–3.5 ng/mL
C1-esterase-inhibitor protein	S	210–390 mg/L	21–39 mg/dL
CA 125	S	<35 kU/L	<35 U/mL
CA 19-9	S	<37 kU/L	<37 U/mL
CA 15-3	S	<33 kU/L	<33 U/mL
CA 27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Male		0–7.5 ng/L	0–7.5 pg/mL
Female		0–5.1 ng/L	0–5.1 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO_2)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers		0.0–0.015	0–1.5%
Smokers		0.04–0.09	4–9%
Loss of consciousness and death		>0.50	>50%
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers		0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol: see Table 5			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chromogranin A	S	0–50 µg/L	0–50 ng/mL
Complement	S		
C3		0.83–1.77 g/L	83–177 mg/dL
C4		0.16–0.47 g/L	16–47 mg/dL
Complement total		60–144 CAE units	60–144 CAE units
Cortisol			
Fasting, 8 A.M.–12 noon	S	138–690 nmol/L	5–25 µg/dL
12 noon–8 P.M.		138–414 nmol/L	5–15 µg/dL
8 P.M.–8 A.M.		0–276 nmol/L	0–10 µg/dL
C-reactive protein	S	<10 mg/L	<10 mg/L
C-reactive protein, high sensitivity	S	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L
Creatine kinase (total)	S		
Females		0.66–4.0 µkat/L	39–238 U/L
Males		0.87–5.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Female		44–80 µmol/L	0.5–0.9 mg/dL
Male		53–106 µmol/L	0.6–1.2 mg/dL
Cryoglobulins	S	Not applicable	None detected
Cystatin C	S	0.5–1.0 mg/L	0.5–1.0 mg/L

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Dehydroepiandrosterone (DHEA) (adult)			
Male	S	6.2–43.4 nmol/L	180–1250 ng/dL
Female		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Male (adult)		100–6190 µg/L	10–619 µg/dL
Female (adult, premenopausal)		120–5350 µg/L	12–535 µg/dL
Female (adult, postmenopausal)		300–2600 µg/L	30–260 µg/dL
11-Deoxycortisol (adult) (compound S)	S	0.34–4.56 nmol/L	12–158 ng/dL
Dihydrotestosterone			
Male	S, P	1.03–2.92 nmol/L	30–85 ng/dL
Female		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	0–130 pmol/L	0–20 pg/mL
Epinephrine	P		
Supine (30 min)		<273 pmol/L	<50 pg/mL
Sitting		<328 pmol/L	<60 pg/mL
Standing (30 min)		<491 pmol/L	<90 pg/mL
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Female			
Menstruating:			
Follicular phase		74–532 pmol/L	<20–145 pg/mL
Midcycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	<20–241 pg/mL
Postmenopausal		217 pmol/L	<59 pg/mL
Male		74 pmol/L	<20 pg/mL
Estrone	S, P		
Female			
Menstruating:			
Follicular phase		<555 pmol/L	<150 pg/mL
Luteal phase		<740 pmol/L	<200 pg/mL
Postmenopausal		11–118 pmol/L	3–32 pg/mL
Male		33–133 pmol/L	9–36 pg/mL
Fatty acids, free (nonesterified)	P	0.1–0.6 mmol/L	2.8–16.8 mg/dL
Ferritin	S		
Female		10–150 µg/L	10–150 ng/mL
Male		29–248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Male		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Fructosamine	S	<285 umol/L	<285 umol/L
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	<100 pg/mL
Glucagon	P	40–130 ng/L	40–130 pg/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Glucose	WB	3.6–5.3 mmol/L	65–95 mg/dL
Glucose (fasting)	P		
Normal		4.2–5.6 mmol/L	75–100 mg/dL
Increased risk for diabetes		5.6–6.9 mmol/L	100–125 mg/dL
Diabetes mellitus		Fasting >7.0 mmol/L A 2-hour level of >11.1 mmol/L during an oral glucose tolerance test A random glucose level of ≥11.1 mmol/L in patients with symptoms of hyperglycemia	Fasting >126 mg/dL A 2-hour level of ≥200 mg/dL during an oral glucose tolerance test A random glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemia
Growth hormone	S	0–5 µg/L	0–5 ng/mL
Hemoglobin A_{1c}	WB	0.04–0.06 HgB fraction	4.0–5.6%
Pre-diabetes		0.057–0.064 HgB fraction	5.7–6.4%
Diabetes mellitus		A hemoglobin A_{1c} level of ≥0.065 Hgb fraction as suggested by the American Diabetes Association	A hemoglobin A_{1c} level of ≥6.5% as suggested by the American Diabetes Association
Hemoglobin A_{1c} with estimated average glucose (eAg)	WB	eAg (mmoL/L) = 1.59 × HbA_{1c} – 2.59	eAg (mg/dL) = 28.7 × HbA_{1c} – 46.7
High-density lipoprotein (HDL) (see Table 5)			
Homocysteine	P	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (HCG)	S		
Nonpregnant female		<5 IU/L	<5 mIU/mL
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks post conception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
β-Hydroxybutyrate	P	60–170 µmol/L	0.6–1.8 mg/dL
17-Hydroxyprogesterone (adult)	S		
Male		<4.17 nmol/L	<139 ng/dL
Female			
Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Immunofixation	S	Not applicable	No bands detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	1–87 kIU/L	1–87 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG_1	S	2.7–17.4 g/L	270–1740 mg/dL
IgG_2	S	0.3–6.3 g/L	30–630 mg/dL
IgG_3	S	0.13–3.2 g/L	13–320 mg/dL
IgG_4	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL
Insulin	S, P	14.35–143.5 pmol/L	2–20 µU/mL
Iron	S	7–25 µmol/L	41–141 µg/dL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Iron-binding capacity	S	45–73 µmol/L	251–406 µg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
Ischemia modified albumin	S	<85 KU/L	<85 U/mL
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Ketone (acetone)	S	Negative	Negative
Lactate	P, arterial P, venous	0.5–1.6 mmol/L 0.5–2.2 mmol/L	4.5–14.4 mg/dL 4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 µkat/L	115–221 U/L
Lipase	S	0.51–0.73 µkat/L	3–43 U/L
Lipids: see Table 5			
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Low-density lipoprotein (LDL) (see Table 5)			
Luteinizing hormone (LH) Female Menstruating Follicular phase Ovulatory phase Luteal phase Postmenopausal Male	S, P 	 2.0–15.0 U/L 22.0–105.0 U/L 0.6–19.0 U/L 16.0–64.0 U/L 2.0–12.0 U/L	 2.0–15.0 mIU/mL 22.0–105.0 mIU/mL 0.6–19.0 mIU/mL 16.0–64.0 mIU/mL 2.0–12.0 mIU/mL
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL
Methemoglobin	WB	0.0–0.01	0–1%
Myoglobin Male Female	S 	 20–71 µg/L 25–58 µg/L	 20–71 µg/L 25–58 µg/L
Norepinephrine Supine (30 min) Sitting Standing (30 min)	P 	 650–2423 pmol/L 709–4019 pmol/L 739–4137 pmol/L	 110–410 pg/mL 120–680 pg/mL 125–700 pg/mL
N-telopeptide (cross-linked), NTx Female, premenopausal Male BCE = bone collagen equivalent	S 	 6.2–19.0 nmol BCE 5.4–24.2 nmol BCE	 6.2–19.0 nmol BCE 5.4–24.2 nmol BCE
NT-Pro BNP	S, P	<125 ng/L up to 75 years <450 ng/L >75 years	<125 pg/mL up to 75 years <450 pg/mL >75 years
5′ Nucleotidase	S	0.00–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mOsmol/kg serum water	275–295 mOsmol/kg serum water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content Arterial (sea level) Venous (sea level)	WB 	 17–21 10–16	 17–21 vol% 10–16 vol%
Oxygen saturation (sea level) Arterial Venous, arm	WB 	Fraction: 0.94–1.0 0.60–0.85	Percent: 94–100% 60–85%
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Phosphatase, alkaline	S	0.56–1.63 μkat/L	33–96 U/L
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin	S	170–340 mg/L	17–34 mg/dL
Procalcitonin	S	<0.1 μg/L	<0.1 ng/mL
Progesterone	S, P		
Female: Follicular		<3.18 nmol/L	<1.0 ng/mL
Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
Male		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S		
Male		53–360 mg/L	2.5–17 ng/mL
Female		40–530 mg/L	1.9–25 ng/mL
Prostate-specific antigen (PSA)	S	0.0–4.0 μg/L	0.0–4.0 ng/mL
Prostate-specific antigen, free	S	With total PSA between 4 and 10 μg/L and when the free PSA is: >0.25 decreased risk of prostate cancer <0.10 increased risk of prostate cancer	With total PSA between 4 and 10 ng/mL and when the free PSA is: >25% decreased risk of prostate cancer <10% increased risk of prostate cancer
Protein fractions:	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
$Alpha_1$		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
$Alpha_2$		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
Beta		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
Gamma		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P	40–130 μmol/L	0.35–1.14 mg/dL
Rheumatoid factor	S	<15 kIU/L	<15 IU/mL
Serotonin	WB	0.28–1.14 umol/L	50–200 ng/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern
Sex hormone–binding globulin (adult)	S		
Male		11–80 nmol/L	11–80 nmol/L
Female		30–135 nmol/L	30–135 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16 years		226–903 μg/L	226–903 ng/mL
17 years		193–731 μg/L	193–731 ng/mL
18 years		163–584 μg/L	163–584 ng/mL
19 years		141–483 μg/L	141–483 ng/mL
20 years		127–424 μg/L	127–424 ng/mL
21–25 years		116–358 μg/L	116–358 ng/mL
26–30 years		117–329 μg/L	117–329 ng/mL
31–35 years		115–307 μg/L	115–307 ng/mL
36–40 years		119–204 μg/L	119–204 ng/mL
41–45 years		101–267 μg/L	101–267 ng/mL
46–50 years		94–252 μg/L	94–252 ng/mL
51–55 years		87–238 μg/L	87–238 ng/mL
56–60 years		81–225 μg/L	81–225 ng/mL
61–65 years		75–212 μg/L	75–212 ng/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
66–70 years		69–200 µg/L	69–200 ng/mL
71–75 years		64–188 µg/L	64–188 ng/mL
76–80 years		59–177 µg/L	59–177 ng/mL
81–85 years		55–166 µg/L	55–166 ng/mL
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, free			
Female, adult	S	10.4–65.9 pmol/L	3–19 pg/mL
Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total,	S		
Female		0.21–2.98 nmol/L	6–86 ng/dL
Male		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	1.3–31.8 µg/L	1.3–31.8 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone	S	0.34–4.25 mIU/L	0.34–4.25 µIU/mL
Thyroxine, free (fT4)	S	9.0–16 pmol/L	0.7–1.24 ng/dL
Thyroxine, total (T4)	S	70–151 nmol/L	5.4–11.7 µg/dL
Thyroxine index (free)	S	6.7–10.9	6.7–10.9
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Triglycerides (see Table 5)	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT3)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T3)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I (method dependent)	S, P		
99th percentile of a healthy population		0–0.04 µg/L	0–0.04 ng/mL
Troponin T	S, P		
99th percentile of a healthy population		0–0.01 µg/L	0–0.01 ng/mL
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Females		0.15–0.33 mmol/L	2.5–5.6 mg/dL
Males		0.18–0.41 mmol/L	3.1–7.0 mg/dL
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL
Zinc protoporphyrin	WB	0–400 µg/L	0–40 µg/dL
Zinc protoporphyrin (ZPP)-to-heme ratio	WB	0–69 µmol ZPP/mol heme	0–69 µmol ZPP/mol heme

Abbreviations: P, plasma; S, serum; WB, whole blood.

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Acetaminophen	66–199 µmol/L	10–30 µg/mL	>1320 µmol/L	>200 µg/mL
Amikacin				
Peak	34–51 µmol/L	20–30 µg/mL	>60 µmol/L	>35 µg/mL
Trough	0–17 µmol/L	0–10 µg/mL	>17 µmol/L	>10 µg/mL
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	9.4–18.7 mmol/L	75–150 mg/dL	>18.8 mmol/L	>150 mg/dL
Mild toxicity			6.4–18.8 mmol/L	51–150 mg/dL
Severe toxicity			>18.8 mmol/L	>150 mg/dL
Lethal			>37.5 mmol/L	>300 mg/dL
Caffeine	25.8–103 µmol/L	5–20 µg/mL	>206 µmol/L	>40 µg/mL
Carbamazepine	17–42 µmol/L	4–10 µg/mL	>85 µmol/L	>20 µg/mL
Chloramphenicol				
Peak	31–62 µmol/L	10–20 µg/mL	>77 µmol/L	>25 µg/mL
Trough	15–31 µmol/L	5–10 µg/mL	>46 µmol/L	>15 µg/mL
Chlordiazepoxide	1.7–10 µmol/L	0.5–3.0 µg/mL	>17µmol/L	>5.0 µg/mL
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 µmol/L	200–700 ng/mL	>3.7 µmol/L	>1200 ng/mL
Cocaine			>3.3 µmol/L	>1.0 µg/mL
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL (lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
Initiation	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
Maintenance	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7–3.5 µmol/L	0.2–1.0 µg/mL	>7.0 µmol/L	>2.0 µg/mL
Nordiazepam	0.4–6.6 µmol/L	0.1–1.8 µg/mL	>9.2 µmol/L	>2.5 µg/mL
Digoxin	0.64–2.6 nmol/L	0.5–2.0 ng/mL	>5.0 nmol/L	>3.9 ng/mL
Disopyramide	5.3–14.7 µmol/L	2–5 µg/mL	>20.6 µmol/L	>7 µg/mL
Doxepin and nordoxepin				
Doxepin	0.36–0.98 µmol/L	101–274 ng/mL	>1.8 µmol/L	>503 ng/mL
Nordoxepin	0.38–1.04 µmol/L	106–291 ng/mL	>1.9 µmol/L	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥17 mmol/L	≥80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL

(*continued*)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (*CONTINUED*)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Everolimus	3.13–8.35 nmol/L	3–8 ng/mL	>12.5 nmol/L	>12 ng/mL
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>970 µmol/L	>200 µg/mL
Imipramine (and metabolite)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total imipramine + desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Lamotrigine	11.7–54.7 µmol/L	3–14 µg/mL	>58.7 µmol/L	>15 µg/mL
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 mmol/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.0–3.2 µmol/L	0.3–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine	0.07–0.34 µmol/L	0.01–0.05 µg/mL	>3.35 µmol/L	>0.5 µg/mL
Methanol			>6 mmol/L	>20 mg/dL
Methotrexate				
Low-dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 mmol/L	>0.1 mmol/L
High-dose (24h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High-dose (48h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High-dose (72h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L
Morphine	232–286 µmol/L	65–80 ng/mL	>720 µmol/L	>200 ng/mL
Mycophenolic acid	3.1–10.9 µmol/L	1.0–3.5 ng/mL	>37 µmol/L	>12 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>258 µmol/L	>60 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>158 µmol/L	>40 µg/mL
Phenytoin, free	4.0–7.9 µg/mL	1–2 µg/mL	>13.9 µg/mL	>3.5 µg/mL
% Free	0.08–0.14	8–14%		
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>43 µmol/L	>10 µg/mL
NAPA (*N*-acetylprocainamide)	22–72 µmol/L	6–20µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	6.2–15.4 µmol/L	2.0–5.0 µg/mL	>19 µmol/L	>6 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2900 µmol/L	>40 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–15.4 nmol/L	4–14 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
Initiation				
Maintenance	6–12 nmol/L	5–10 ng/mL	>25 nmol/L	>20 ng/mL
Heart				
Initiation	19–25 nmol/L	15–20 ng/mL		
Maintenance	6–12 nmol/L	5–10 ng/mL		

(*continued*)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (*CONTINUED*)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Theophylline	56–111 µg/mL	10–20 µg/mL	>168 µg/mL	>30 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Valproic acid	346–693 µmol/L	50–100 µg/mL	>693 µmol/L	>100 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55 µmol/L	>80 µg/mL
Trough	3.5–10.4 µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL

TABLE 4

VITAMINS AND SELECTED TRACE MINERALS

		REFERENCE RANGE	
SPECIMEN	**ANALYTE**	**SI UNITS**	**CONVENTIONAL UNITS**
Aluminum	S	<0.2 µmol/L	<5.41 µg/L
Arsenic	WB	0.03–0.31 µmol/L	2–23 µg/L
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L
β-Carotene	S	0.07–1.43 µmol/L	4–77 µg/dL
Copper	S	11–22 µmol/L	70–140 µg/dL
Folic acid	RC	340–1020 nmol/L cells	150–450 ng/mL cells
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL
Lead (adult)	S	<0.5 µmol/L	<10 µg/dL
Mercury	WB	3.0–294 nmol/L	0.6–59 µg/L
Selenium	S	0.8–2.0 umol/L	63–160 µg/L
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL
Vitamin B_1 (thiamine)	S	0–75 nmol/L	0–2 µg/dL
Vitamin B_2 (riboflavin)	S	106–638 nmol/L	4–24 µg/dL
Vitamin B_6	P	20–121 nmol/L	5–30 ng/mL
Vitamin B_{12}	S	206–735 pmol/L	279–996 pg/mL
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL
Vitamin D_3,1,25-dihydroxy, total	S, P	36–180 pmol/L	15–75 pg/mL
Vitamin D_3, 25-hydroxy, total	P	75–250 nmol/L	30–100 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL

Abbreviations: P, plasma; RC, red cells; S, serum; WB, whole blood.

TABLE 5

CLASSIFICATION OF LDL, TOTAL, AND HDL CHOLESTEROL

LDL Cholesterol	
<70 mg/dL	Therapeutic option for very high risk patients
<100 mg/dL	Optimal
100–129 mg/dL	Near optimal/above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
Total Cholesterol	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
≥240 mg/dL	High
HDL Cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Source: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001; 285:2486–97. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. SM Grundy et al for the Coordinating Committee of the National Cholesterol Education Program: Circulation 110:227, 2004.

REFERENCE VALUES FOR SPECIFIC ANALYTES

TABLE 6

CEREBROSPINAL FLUID[a]

	REFERENCE RANGE	
CONSTITUENT	**SI UNITS**	**CONVENTIONAL UNITS**
Osmolarity	292–297 mmol/kg water	292–297 mOsm/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO_2 content	20–24 mmol/L	20–24 meq/L
P_{CO_2}	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein:		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 µmol/L	25–80 µg/dL
Creatinine	44–168 µmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 µg/L	
CSF pressure		50–180 mmH_2O
CSF volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per µL	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a]Since cerebrospinal fluid concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase.

[b]IgG index = CSF IgG (mg/dL) × serum albumin (g/dL)/serum IgG (g/dL) × CSF albumin (mg/dL).

TABLE 7A

DIFFERENTIAL NUCLEATED CELL COUNTS OF BONE MARROW ASPIRATES[a]

	OBSERVED RANGE (%)	95% RANGE (%)	MEAN (%)
Blast cells	0–3.2	0–3.0	1.4
Promyelocytes	3.6–13.2	3.2–12.4	7.8
Neutrophil myelocytes	4–21.4	3.7–10.0	7.6
Eosinophil myelocytes	0–5.0	0–2.8	1.3
Metamyelocytes	1–7.0	2.3–5.9	4.1
Neutrophils			
Males	21.0–45.6	21.9–42.3	32.1
Females	29.6–46.6	28.8–45.9	37.4
Eosinophils	0.4–4.2	0.3–4.2	2.2
Eosinophils plus eosinophil myelocytes	0.9–7.4	0.7–6.3	3.5
Basophils	0–0.8	0–0.4	0.1
Erythroblasts			
Male	18.0–39.4	16.2–40.1	28.1
Females	14.0–31.8	13.0–32.0	22.5
Lymphocytes	4.6–22.6	6.0–20.0	13.1
Plasma cells	0–1.4	0–1.2	0.6
Monocytes	0–3.2	0–2.6	1.3
Macrophages	0–1.8	0–1.3	0.4
M:E ratio			
Males	1.1–4.0	1.1–4.1	2.1
Females	1.6–5.4	1.6–5.2	2.8

[a]Based on bone marrow aspirate from 50 healthy volunteers (30 men, 20 women).
Abbreviation: M:E, myeloid to erythroid ratio.
Source: BJ Bain: Br J Haematol 94:206, 1996.

TABLE 7B

BONE MARROW CELLULARITY

AGE	OBSERVED RANGE	95% RANGE	MEAN
Under 10 years	59.0–95.1%	72.9–84.7%	78.8%
10–19 years	41.5–86.6%	59.2–69.4%	64.3%
20–29 years	32.0–83.7%	54.1–61.9%	58.0%
30–39 years	30.3–81.3%	41.1–54.1%	47.6%
40–49 years	16.3–75.1%	43.5–52.9%	48.2%
50–59 years	19.7–73.6%	41.2–51.4%	46.3%
60–69 years	16.3–65.7%	40.8–50.6%	45.7%
70–79 years	11.3–47.1%	22.6–35.2%	28.9%

Source: From RJ Hartsock et al: Am J Clin Pathol 1965; 43:326, 1965.

TABLE 8

STOOL ANALYSIS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Alpha-1-antitrypsin	≤540 mg/L	≤54 mg/dL
Amount	0.1–0.2 kg/d	100–200 g/24 h
Coproporphyrin	611–1832 nmol/d	400–1200 μg/24 h
Fat		
Adult		<7 g/d
Adult on fat-free diet		<4 g/d
Fatty acids	0–21 mmol/d	0–6 g/24 h
Leukocytes	None	None
Nitrogen	<178 mmol/d	<2.5 g/24 h
pH	7.0–7.5	
Potassium	14–102 mmol/L	14–102 mmol/L
Occult blood	Negative	Negative
Osmolality	280–325 mosmol/kg	280–325 mosmol/kg
Sodium	7–72 mmol/L	7–72 mmol/L
Trypsin		20–95 U/g
Urobilinogen	85–510 μmol/d	50–300 mg/24 h
Uroporphyrins	12–48 nmol/d	10–40 μg/24 h
Water	<0.75	<75%

Source: Modified from: FT Fishbach, MB Dunning III: *A Manual of Laboratory and Diagnostic Tests*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2004.

TABLE 9

URINE ANALYSIS AND RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Aldosterone	Normal diet: 6–25 μg/d Low-salt diet: 17–44 μg/d High-salt diet: 0–6 μg/d	Normal diet: 6–25 μg/d Low-salt diet: 17–44 μg/d High-salt diet: 0–6 μg/d
Aluminum	0.19–1.11 μmol/L	5–30 μg/L
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio [$(Cl_{am}/Cl_{cr}) \times 100$]	1–5	1–5
Arsenic	0.07–0.67 μmol/d	5–50 μg/d
Bence Jones protein, urine, qualitative	Not applicable	None detected
Bence Jones protein, urine, quantitative		
Free Kappa	1.4–24.2 mg/L	0.14–2.42 mg/dL
Free Lambda	0.2–6.7 mg/L	0.02–0.67 mg/dL
K/L ratio	2.04–10.37	2.04–10.37
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Chloride	140–250 mmol/d	140–250 mmol/d
Citrate	320–1240 mg/d	320–1240 mg/d
Copper	<0.95 μmol/d	<60 μg/d
Coproporphyrins (types I and III)	0–20 μmol/mol creatinine	0–20 μmol/mol creatinine
Cortisol, free	55–193 nmol/d	20–70 μg/d
Creatine, as creatinine		
Female	<760 μmol/d	<100 mg/d
Male	<380 μmol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Dopamine	392–2876 nmol/d	60–440 μg/d
Eosinophils	<100 eosinophils/mL	<100 eosinophils/mL
Epinephrine	0–109 nmol/d	0–20 μg/d
Glomerular filtration rate	>60 mL/min/1.73 m^2 For African Americans multiply the result by 1.21	>60 mL/min/1.73 m^2 For African Americans multiply the result by 1.21
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroindoleacetic acid [5-HIAA]	0–78.8 μmol/d	0–15 mg/d
Hydroxyproline	53–328 μmol/d	53–328 μmol/d
Iodine, spot urine		
WHO classification of iodine deficiency:		
Not iodine deficient	>100 μg/L	>100 μg/L
Mild iodine deficiency	50–100 μg/L	50–100 μg/L
Moderate iodine deficiency	20–49 μg/L	20–49 μg/L
Severe iodine deficiency	<20 μg/L	<20 μg/L
Ketone (acetone)	Negative	Negative
17 Ketosteroids	3–12 mg/d	3–12 mg/d
Metanephrines		
Metanephrine	30–350 μg/d	30–350 μg/d
Normetanephrine	50–650 μg/d	50–650 μg/d

(*continued*)

TABLE 9

URINE ANALYSIS AND RENAL FUNCTION TESTS (*CONTINUED*)

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 µg/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 µg/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 µg/mg creatinine
β_2-Microglobulin	0–160 µg/L	0–160 µg/L
Norepinephrine	89–473 nmol/d	15–80 µg/d
N-telopeptide (cross-linked), NTx		
Female, premenopausal	17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Female, postmenopausal	26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Male	21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
BCE = bone collagen equivalent		
Osmolality	100–800 mosm/kg	100–800 mosm/kg
Oxalate		
Male	80–500 µmol/d	7–44 mg/d
Female	45–350 µmol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Porphobilinogen	None	None
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Protein/creatinine ratio	Male: 15–68 mg/g Female: 10–107 mg/g	Male: 15–68 mg/g Female: 10–107 mg/g
Sediment		
Red blood cells	0–2/high-power field	
White blood cells	0–2/high-power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	
Hyaline casts	0–5/low-power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity:		
After 12-h fluid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)	<30 µmol/d	<6 mg/d

TABLE 10

NORMAL PRESSURES IN HEART AND GREAT VESSELS

PRESSURE (mmHg)	AVERAGE	RANGE
Right Atrium		
Mean	2.8	1–5
a wave	5.6	2.5–7
c wave	3.8	1.5–6
x wave	1.7	0–5
v wave	4.6	2–7.5
y wave	2.4	0–6
Right Ventricle		
Peak systolic	25	17–32
End-diastolic	4	1–7
Pulmonary Artery		
Mean	15	9–19
Peak systolic	25	17–32
End-diastolic	9	4–13
Pulmonary Artery Wedge		
Mean	9	4.5–13
Left Atrium		
Mean	7.9	2–12
a wave	10.4	4–16
v wave	12.8	6–21
Left Ventricle		
Peak systolic	130	90–140
End-diastolic	8.7	5–12
Brachial Artery		
Mean	85	70–105
Peak systolic	130	90–140
End-diastolic	70	60–90

Source: Reproduced from: MJ Kern *The Cardiac Catheterization Handbook*, 4th ed. Philadelphia, Mosby, 2003.

TABLE 11

CIRCULATORY FUNCTION TESTS

TEST	RESULTS: REFERENCE RANGE	
	SI UNITS (RANGE)	CONVENTIONAL UNITS (RANGE)
Arteriovenous oxygen difference	30–50 mL/L	30–50 mL/L
Cardiac output (Fick)	2.5–3.6 L/m^2 of body surface area per min	2.5–3.6 L/m^2 of body surface area per min
Contractility indexes		
Max. left ventricular *dp*/*dt* (*dp*/*dt*)	220 kPa/s (176–250 kPa/s)	1650 mmHg/s (1320–1880 mmHg/s)
DP when DP = 5.3 kPa	(37.6 ± 12.2)/s	(37.6 ± 12.2)/s
(40 mmHg) (DP, developed LV pressure)	3.32 ± 0.84 end-diastolic volumes per second	3.32 ± 0.84 end-diastolic volumes per second
Mean normalized systolic ejection rate (angiography)	1.83 ± 0.56 circumferences per second	1.83 ± 0.56 circumferences per second
Mean velocity of circumferential fiber shortening (angiography)		
Ejection fraction: stroke volume/ end-diastolic volume (SV/EDV)	0.67 ± 0.08 (0.55–0.78)	0.67 ± 0.08 (0.55–0.78)
End-diastolic volume	70 ± 20.0 mL/m^2 (60–88 mL/m^2)	70 ± 20.0 mL/m^2 (60–88 mL/m^2)
End-systolic volume	25 ± 5.0 mL/m^2 (20–33 mL/m^2)	25 ± 5.0 mL/m^2 (20–33 mL/m^2)
Left ventricular work		
Stroke work index	50 ± 20.0 (g·m)/m^2 (30–110)	50 ± 20.0 (g·m)/m^2 (30–110)
Left ventricular minute work index	1.8–6.6 [(kg·m)/m^2]/min	1.8–6.6 [(kg·m)/m^2]/min
Oxygen consumption index	110–150 mL	110–150 mL
Maximum oxygen uptake	35 mL/min (20–60 mL/min)	35 mL/min (20–60 mL/min)
Pulmonary vascular resistance	2–12 (kPa·s)/L	20–130 (dyn·s)/cm^5
Systemic vascular resistance	77–150 (kPa·s)/L	770–1600 (dyn·s)/cm^5

Source: E Braunwald et al: *Heart Disease*, 6th ed. Philadelphia, W.B. Saunders Co., 2001.

TABLE 12

NORMAL ECHOCARDIOGRAPHIC REFERENCE LIMITS AND PARTITION VALUES IN ADULTS

	WOMEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL	MEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL
Left ventricular dimensions								
Septal thickness, cm	0.6–0.9	1.0–1.2	1.3–1.5	≥1.6	0.6–1.0	1.1–1.3	1.4–1.6	≥1.7
Posterior wall thickness, cm	0.6–0.9	1.0–1.2	1.3–1.5	≥1.6	0.6–1.0	1.1–1.3	1.4–1.6	≥1.7
Diastolic diameter, cm	3.9–5.3	5.4–5.7	5.8–6.1	≥6.2	4.2–5.9	6.0–6.3	6.4–6.8	≥6.9
Diastolic diameter/BSA, cm/m^2	2.4–3.2	3.3–3.4	3.5–3.7	≥3.8	2.2–3.1	3.2–3.4	3.5–3.6	≥3.7
Diastolic diameter/height, cm/m	2.5–3.2	3.3–3.4	3.5–3.6	≥3.7	2.4–3.3	3.4–3.5	3.6–3.7	≥3.8
Left ventricular volumes								
Diastolic, mL	56–104	105–117	118–130	≥131	67–155	156–178	179–201	≥202
Diastolic/BSA, mL/m^2	35–75	76–86	87–96	≥97	35–75	76–86	87–96	≥97
Systolic, mL	19–49	50–59	60–69	≥70	22–58	59–70	71–82	≥83
Systolic/BSA, mL/m^2	12–30	31–36	37–42	≥43	12–30	31–36	37–42	≥43
Left ventricular mass, 2D method								
Mass, g	66–150	151–171	172–182	≥183	96–200	201–227	228–254	≥255
Mass/BSA, g/m^2	44–88	89–100	101–112	≥113	50–102	103–116	117–130	≥131
Left ventricular function								
Endocardial fractional shortening (%)	27–45	22–26	17–21	≤16	25–43	20–24	15–19	≤14
Midwall fractional shortening (%)	15–23	13–14	11–12	≤10	14–22	12–13	10–11	≤9
Ejection fraction, 2D method (%)	≥55	45–54	30–44	≤29	≥55	45–54	30–44	≤29
Right heart dimensions (cm)								
Basal RV diameter	2.0–2.8	2.9–3.3	3.4–3.8	≥3.9	2.0–2.8	2.9–3.3	3.4–3.8	≥3.9
Mid-RV diameter	2.7–3.3	3.4–3.7	3.8–4.1	≥4.2	2.7–3.3	3.4–3.7	3.8–4.1	≥4.2
Base-to-apex length	7.1–7.9	8.0–8.5	8.6–9.1	≥9.2	7.1–7.9	8.0–8.5	8.6–9.1	≥9.2
RVOT diameter above aortic valve	2.5–2.9	3.0–3.2	3.3–3.5	≥3.6	2.5–2.9	3.0–3.2	3.3–3.5	≥3.6
RVOT diameter above pulmonic valve	1.7–2.3	2.4–2.7	2.8–3.1	≥3.2	1.7–2.3	2.4–2.7	2.8–3.1	≥3.2
Pulmonary artery diameter below pulmonic valve	1.5–2.1	2.2–2.5	2.6–2.9	≥3.0	1.5–2.1	2.2–2.5	2.6–2.9	≥3.0
Right ventricular size and function in 4-chamber view								
Diastolic area, cm^2	11–28	29–32	33–37	≥38	11–28	29–32	33–37	≥38
Systolic area, cm^2	7.5–16	17–19	20–22	≥23	7.5–16	17–19	20–22	≥23
Fractional area change, %	32–60	25–31	18–24	≤17	32–60	25–31	18–24	≤17
Atrial sizes								
LA diameter, cm	2.7–3.8	3.9–4.2	4.3–4.6	≥4.7	3.0–4.0	4.1–4.6	4.7–5.2	≥5.3
LA diameter/BSA, cm/m^2	1.5–2.3	2.4–2.6	2.7–2.9	≥3.0	1.5–2.3	2.4–2.6	2.7–2.9	≥3.0
RA minor axis, cm	2.9–4.5	4.6–4.9	5.0–5.4	≥5.5	2.9–4.5	4.6–4.9	5.0–5.4	≥5.5
RA minor axis/BSA, cm/m^2	1.7–2.5	2.6–2.8	2.9–3.1	≥3.2	1.7–2.5	2.6–2.8	2.9–3.1	≥3.2

(*continued*)

TABLE 12

NORMAL ECHOCARDIOGRAPHIC REFERENCE LIMITS AND PARTITION VALUES IN ADULTS (*CONTINUED*)

	WOMEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL	MEN REFERENCE RANGE	MILDLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL
LA area, cm^2	<20	20–30	30–40	≥41	<20	20–30	30–40	≥41
LA volume, mL	22–52	53–62	63–72	≥73	18–58	59–68	69–78	≥79
LA volume/BSA, mL/m^2	16–28	29–33	34–39	≥40	16–28	29–33	34–39	≥40
Aortic stenosis, classification of severity								
Aortic jet velocity, m/s		2.6–2.9	3.0–4.0	>4.0		2.6–2.9	3.0–4.0	>4.0
Mean gradient, mmHg		<20	20–40	>40		<20	20–40	>40
Valve area, cm^2		>1.5	1.0–1.5	<1.0		>1.5	1.0–1.5	<1.0
Indexed valve area, cm^2/m^2		>0.85	0.60–0.85	<0.6		>0.85	0.60–0.85	<0.6
Velocity ratio		>0.50	0.25–0.50	<0.25		>0.50	0.25–0.50	<0.25
Mitral stenosis, classification of severity								
Valve area, cm^2		>1.5	1.0–1.5	<1.0		>1.5	1.0–1.5	<1.0
Mean gradient, mmHg		<5	5–10	>10		<5	5–10	>10
Pulmonary artery pressure, mmHg		<30	30–50	>50		<30	30–50	>50
Aortic regurgitation, indices of severity								
Vena contracta width, cm		<0.30	0.30–0.60	≥0.60		<0.30	0.30–0.60	≥0.60
Jet width/LVOT width, %		<25	25–64	≥65		<25	25–64	≥65
Jet CSA/LVOT CSA, %		<5	5–59	≥60		<5	5–59	≥60
Regurgitant volume, mL/beat		<30	30–59	≥60		<30	30–59	≥60
Regurgitant fraction, %		<30	30–49	≥50		<30	30–49	≥50
Effective regurgitant orifice area, cm^2		<0.10	0.10–0.29	≥0.30		<0.10	0.10–0.29	≥0.30
Mitral regurgitation, indices of severity								
Vena contracta width, cm		<0.30	0.30–0.69	≥0.70		<0.30	0.30–0.69	≥0.70
Regurgitant volume, mL/beat		<30	30–59	≥60		<30	30–59	≥60
Regurgitant fraction, %		<30	30–49	≥50		<30	30–49	≥50
Effective regurgitant orifice area, cm^2		<0.20	0.20–0.39	≥0.40		<0.20	0.20–0.39	≥0.40

Abbreviations: BSA, body surface area; CSA, cross-sectional area; LA, left atrium; LVOT, left ventricular outflow tract; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; 2D, 2-dimensional.

Source: Values adapted from: American Society of Echocardiography, Guidelines and Standards. *http://www.asecho.org/i4a/pages/index.cfm?pageid=3317*. Accessed Feb 23, 2010.

TABLE 13

SUMMARY OF VALUES USEFUL IN PULMONARY PHYSIOLOGY

	SYMBOL	TYPICAL VALUES	
		MAN AGED 40, 75 kg, 175 cm TALL	WOMAN AGED 40, 60 kg, 160 cm TALL
Pulmonary Mechanics			
Spirometry—volume-time curves			
Forced vital capacity	FVC	5.0 L	3.4 L
Forced expiratory volume in 1 s	FEV_1	4.0 L	2.8 L
FEV_1/FVC	FEV_1%	80%	78%
Maximal midexpiratory flow rate	MMEF (FEF 25–75)	4.1 L/s	3.2 L/s
Maximal expiratory flow rate	MEFR (FEF 200–1200)	9.0 L/s	6.1 L/s
Spirometry—flow-volume curves			
Maximal expiratory flow at 50% of expired vital capacity	V_{max} 50 (FEF 50%)	5.0 L/s	4.0 L/s
Maximal expiratory flow at 75% of expired vital capacity	V_{max} 75 (FEF 75%)	2.1 L/s	2.0 L/s
Resistance to airflow:			
Pulmonary resistance	RL (R_L)	<3.0 (cmH_2O/s)/L	
Airway resistance	Raw	<2.5 (cmH_2O/s)/L	
Specific conductance	SGaw	>0.13 cmH_2O/s	
Pulmonary compliance			
Static recoil pressure at total lung capacity	Pst TLC	25 ± 5 cmH_2O	
Compliance of lungs (static)	CL	0.2 L cmH_2O	
Compliance of lungs and thorax	C(L + T)	0.1 L cmH_2O	
Dynamic compliance of 20 breaths per minute	C dyn 20	0.25 ± 0.05 L/cmH_2O	
Maximal static respiratory pressures:			
Maximal inspiratory pressure	MIP	>110 cmH_2O	>70 cmH_2O
Maximal expiratory pressure	MEP	>200 cmH_2O	>140 cmH_2O
Lung Volumes			
Total lung capacity	TLC	6.9 L	4.9 L
Functional residual capacity	FRC	3.3 L	2.6 L
Residual volume	RV	1.9 L	1.5 L
Inspiratory capacity	IC	3.7 L	2.3 L
Expiratory reserve volume	ERV	1.4 L	1.1 L
Vital capacity	VC	5.0 L	3.4 L
Gas Exchange (Sea Level)			
Arterial O_2 tension	Pa_{O_2}	12.7 ± 0.7 kPa (95 ± 5 mmHg)	
Arterial CO_2 tension	Pa_{CO_2}	5.3 ± 0.3 kPa (40 ± 2 mmHg)	
Arterial O_2 saturation	Sa_{O_2}	0.97 ± 0.02 (97 ± 2%)	
Arterial blood pH	pH	7.40 ± 0.02	
Arterial bicarbonate	HCO_3^-	24 + 2 meq/L	
Base excess	BE	0 ± 2 meq/L	
Diffusing capacity for carbon monoxide (single breath)	DL_{CO}	37 mL CO/min/mmHg	27 mL CO/min/mmHg
Dead space volume	V_D	2 mL/kg body wt	
Physiologic dead space; dead space-tidal volume ratio	V_D/V_T		
Rest		≤35% V_T	
Exercise		≤20% V_T	
Alveolar-arterial difference for O_2	$P(A - a)_{O2}$	≤2.7 kPa ≤20 kPa (≤24 mmHg)	

Source: Based on: AH Morris et al: *Clinical Pulmonary Function Testing. A Manual of Uniform Laboratory Procedures*, 2nd ed. Salt Lake City, Utah, Intermountain Thoracic Society, 1984.

TABLE 14

GASTROINTESTINAL TESTS

TEST	RESULTS	
	SI UNITS	CONVENTIONAL UNITS
Absorption tests		
D-Xylose: after overnight fast, 25 g xylose given in oral aqueous solution		
Urine, collected for following 5 h	25% of ingested dose	25% of ingested dose
Serum, 2 h after dose	2.0–3.5 mmol/L	30–52 mg/dL
Vitamin A: a fasting blood specimen is obtained and 200,000 units of vitamin A in oil is given orally	Serum level should rise to twice fasting level in 3–5 h	Serum level should rise to twice fasting level in 3–5 h
Bentiromide test (pancreatic function): 500 mg bentiromide (chymex) orally; *p*-aminobenzoic acid (PABA) measured		
Plasma		>3.6 (±1.1) µg/mL at 90 min
Urine	>50% recovered in 6 h	>50% recovered in 6 h
Gastric juice		
Volume		
24 h	2–3 L	2–3 L
Nocturnal	600–700 mL	600–700 mL
Basal, fasting	30–70 mL/h	30–70 mL/h
Reaction		
pH	1.6–1.8	1.6–1.8
Titratable acidity of fasting juice	4–9 µmol/s	15–35 meq/h
Acid output		
Basal		
Females (mean ± 1 SD)	0.6 ± 0.5 µmol/s	2.0 ± 1.8 meq/h
Males (mean ± 1 SD)	0.8 ± 0.6 µmol/s	3.0 ± 2.0 meq/h
Maximal (after SC histamine acid phosphate, 0.004 mg/kg body weight, and preceded by 50 mg promethazine, or after betazole, 1.7 mg/kg body weight, or pentagastrin, 6 µg/kg body weight)		
Females (mean ± 1 SD)	4.4 ± 1.4 µmol/s	16 ± 5 meq/h
Males (mean ± 1 SD)	6.4 ± 1.4 µmol/s	23 ± 5 meq/h
Basal acid output/maximal acid output ratio	≤0.6	≤0.6
Gastrin, serum	0–200 µg/L	0–200 pg/mL
Secretin test (pancreatic exocrine function): 1 unit/kg body weight, IV		
Volume (pancreatic juice) in 80 min	>2.0 mL/kg	>2.0 mL/kg
Bicarbonate concentration	>80 mmol/L	>80 meq/L
Bicarbonate output in 30 min	>10 mmol	>10 meq

MISCELLANEOUS

TABLE 15
BODY FLUIDS AND OTHER MASS DATA

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Ascitic fluid		
Body fluid		
Total volume (lean) of body weight	50% (in obese) to 70%	
Intracellular	30-40% of body weight	
Extracellular	20-30% of body weight	
Blood		
Total volume		
Males	69 mL/kg body weight	
Females	65 mL/kg body weight	
Plasma volume		
Males	39 mL/kg body weight	
Females	40 mL/kg body weight	
Red blood cell volume		
Males	30 mL/kg body weight	1.15–1.21 L/m^2 of body surface area
Females	25 mL/kg body weight	0.95–1.00 L/m^2 of body surface area
Body mass index	18.5–24.9 kg/m^2	18.5–24.9 kg/m^2

TABLE 16
RADIATION-DERIVED UNITS

QUANTITY	MEASURES	OLD UNIT	SI UNIT	SPECIAL NAME FOR SI UNIT (ABBREVIATION)	CONVERSION
Activity	Rate of radioactive decay	curie (Ci)	Disintegrations per second (dps)	becquerel (Bq)	1 Ci = 3.7×10^{10} Bq 1 mCi = 37 MBq 1 Bq = 2.703×10^{-11} Ci
Exposure	Amount of ionizations produced in dry air by x-rays or gamma rays, per unit of mass	roentgen (R)	Coulomb per kilogram (C/kg)	none	1 C/kg = 3876 R 1 R = 2.58×10^{-4} C/kg 1 mR = 258 pC/kg
Air kerma	Sum of initial energies of charged particles liberated by ionizing radiation in air, per unit of mass	rad	Joule per kilogram (J/kg)	gray (Gy)	1 Gy = 100 rad 1 rad = 0.01 Gy 1 mrad = 10 μGy
Absorbed dose	Energy deposited per unit of mass in a medium, e.g., an organ/tissue	rad	Joule per kilogram (J/kg)	gray (Gy)	1 Gy = 100 rad 1 rad = 0.01 Gy 1 mrad = 10 μGy
Equivalent dose	Energy deposited per unit of mass in a medium, e.g., an organ/tissue, weighted to reflect type(s) of radiation	rem	Joule per kilogram (J/kg)	sievert (Sv)	1 Sv = 100 rem 1 rem = 0.01 Sv 1 mrem = 10 μSv
Effective dose	Energy deposited per unit of mass in a reference individual, doubly weighted to reflect type(s) of radiation and organ(s) irradiated	rem	Joule per kilogram (J/kg)	sievert (Sv)	1 Sv = 100 rem 1 rem = 0.01 Sv 1 mrem = 10 μSv

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REVIEW AND SELF-ASSESSMENT[a]

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QUESTIONS

DIRECTIONS: Choose the **one best** response to each question.

1. All of the following are key features of the innate immune system EXCEPT:

A. Exclusively a feature of vertebrate animals
B. Important cells include macrophages and natural killer lymphocytes
C. Nonrecognition of benign foreign molecules or microbes
D. Recognition by germ line–encoded host molecules
E. Recognition of key microbe virulence factors but not recognition of self molecules

2. A 29-year-old male with episodic abdominal pain and stress-induced edema of the lips, the tongue, and occasionally the larynx is likely to have low functional or absolute levels of which of the following proteins?

A. C1 esterase inhibitor
B. C5A (complement cascade)
C. Cyclooxygenase
D. IgE
E. T-cell receptor, α chain

3. Which of the following statements best describes the function of proteins encoded by the human major histocompatibility complex (MHC) I and II genes?

A. Activation of the complement system
B. Binding to cell surface receptors on granulocytes and macrophages to initiate phagocytosis
C. Nonspecific binding of antigen for presentation to T cells
D. Specific antigen binding in response to B-cell activation to promote neutralization and precipitation

4. Which of the following autoantibodies is most likely to be present in a patient with systemic lupus erythematosus?

4. (*Continued*)
A. Anti-dsDNA
B. Anti-RNP
C. Anti-Ro
D. Antiphospholipid
E. Antiribosomal P

5. A 23-year-old woman is evaluated by her primary care physician because she is concerned that she may have systemic lupus erythematosus after hearing a public health announcement on the radio. She has no significant past medical history, and her only medication is occasional ibuprofen. She is not sexually active and works in a grocery store. She reports that she has had intermittent oral ulcers and right knee pain. Physical examination shows no evidence of alopecia, skin rash, or joint swelling/inflammation. Her blood work shows that she has a positive antinuclear antibody (ANA) at a titer of 1:40, but no other abnormalities. Which of the following statements is true?

A. Four diagnostic criteria are required to meet the criteria for systemic lupus erythematosus; this patient has three.
B. Four diagnostic criteria are required to meet the criteria for systemic lupus erythematosus; this patient has two.
C. If a urinalysis shows proteinuria, she will meet the criteria for systemic lupus erythematosus.
D. She meets the criteria for systemic lupus erythematosus because she has three criteria for the disease.
E. The demonstration of a positive ANA alone is adequate to diagnose systemic lupus erythematosus.

6. A 32-year-old woman with a long-standing diagnosis of systemic lupus erythematosus is evaluated by her rheumatologist as routine follow-up. A new cardiac murmur is heard and an echocardiogram is ordered. She is feeling well, and has no fevers, weight loss, or preexisting cardiac disease. A vegetation on the mitral valve is demonstrated. Which of the following statements is true?

[a]Questions and answers were taken from Wiener C et al (eds): *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 18th ed. New York: McGraw-Hill, 2012.

6. (*Continued*)

A. Blood cultures are unlikely to be positive.
B. Glucocorticoid therapy has been proven to lead to improvement in this condition.
C. Pericarditis is frequently present concomitantly.
D. The lesion has a low risk of embolization.
E. The patient has been surreptitiously using injection drugs.

7. A 24-year-old woman is newly diagnosed with systemic lupus erythematosus. Which of the following organ system complications is she most likely to have over the course of her lifetime?

A. Cardiopulmonary
B. Cutaneous
C. Hematologic
D. Musculoskeletal
E. Renal

8. A 27-year-old female with systemic lupus erythematosus (SLE) is in remission; current treatment consists of azathioprine 75 mg/d and prednisone 5 mg/d. Last year she had a life-threatening exacerbation of her disease. She now strongly desires to become pregnant. Which of the following is the least appropriate action to take?

A. Advise her that the risk of spontaneous abortion is high.
B. Warn her that exacerbations can occur in the first trimester and in the postpartum period.
C. Tell her it is unlikely that a newborn will have lupus.
D. Advise her that fetal loss rates are higher if anticardiolipin antibodies are detected in her serum.
E. Stop the prednisone just before she attempts to become pregnant.

9. A 45-year-old African-American woman with systemic lupus erythematosus (SLE) presents to the emergency department with complaints of headache and fatigue. Her prior manifestations of SLE have been arthralgias, hemolytic anemia, malar rash, and mouth ulcers, and she is known to have high titers of antibodies to double-stranded DNA. She currently is taking prednisone, 5 mg daily, and hydroxychloroquine, 200 mg daily. On presentation, she is found to have a blood pressure of 190/110 mmHg with a heart rate of 98 beats/min. A urinalysis shows 25 red blood cells (RBCs) per high-power field with 2+ proteinuria. No RBC casts are identified. Her blood urea nitrogen is 88 mg/dL, and creatinine is 2.6 mg/dL (baseline 0.8 mg/dL). She has not previously had renal disease related to SLE and is not taking nonsteroidal

9. (*Continued*)

anti-inflammatory drugs. She denies any recent illness, decreased oral intake, or diarrhea. What is the most appropriate next step in the management of this patient?

A. Initiate cyclophosphamide, 500 mg/m^2 body surface area IV, and plan to repeat monthly for 3–6 months.
B. Initiate hemodialysis.
C. Initiate high-dose steroid therapy (IV methylprednisolone, 1000 mg daily for 3 doses, followed by oral prednisone, 1 mg/kg daily) and mycophenolate mofetil, 2 g daily.
D. Initiate plasmapheresis.
E. Withhold all therapy until renal biopsy is performed.

10. A 25-year-old African-American woman was has been followed in SLE clinic since her diagnosis 6 months ago. At that time she had evidence of mild joint disease, photosensitivity, malar rash, positive ANA, and anti-dsDNA. Her renal function and urinalysis were normal. She has been maintained on acetaminophen and hydroxychloroquine. She comes to the emergency department after a recent outing to the beach with friends. Over the past 2 days she's noticed a marked increase in her fatigue and morning stiffness. She also has red-tinged urine. Physical examination is notable for a skin rash in sun-exposed areas, and diffuse wrist, knee, and ankle synovial thickening. Her platelet count has fallen from normal values to 45,000 and she has new leukopenia. In addition, her serum creatinine is 2.5 and there are RBC casts on urine analysis. An emergent renal biopsy is consistent with active diffuse lupus nephritis. After receiving methylprednisolone 1 g IV for 3 days, all of the following are appropriate treatment regimens EXCEPT:

A. Prednisone 60 mg/d
B. Prednisone 60 mg/d plus azathioprine
C. Prednisone 60 mg/d plus cyclophosphamide
D. Prednisone 60 mg/d plus mycophenolate mofetil
E. Rituximab

11. A 27-year-old woman is admitted to the intensive care unit after delivery of a full-term infant 3 days prior. The patient was found to have right hemiparesis and a blue left hand. Physical examination is also notable for livedo reticularis. Her laboratories were notable for a white blood cell count of 10.2/mL, hematocrit 35%, and platelet count of 13,000/mL. Her BUN is 36 mg/dL and her creatinine is 2.3 mg/dL. Although this pregnancy was uneventful, the three prior pregnancies resulted in early losses. A peripheral smear shows

11. (*Continued*)
no evidence of schistocytes. Which of the following laboratory studies will best confirm the underlying etiology of her presentation?

A. Anticardiolipin antibody panel
B. Antinuclear antibody
C. Doppler examination of her left arm arterial tree
D. Echocardiography
E. MRI of her brain

12. A 28-year-old woman comes to the emergency department complaining of 1 day of worsening right leg pain and swelling. She drove in a car for 8 hours returning from a hiking trip 2 days ago then noticed some pain in the leg. At first she thought it was due to exertion but it has worsened over the day. Her only past medical history is related to difficulty getting pregnant with 2 prior spontaneous abortions. Her physical examination is notable for normal vital signs and heart and lung examination. Her right leg is swollen from the mid-thigh down and is tender. Doppler studies demonstrate a large deep venous thrombosis in the femoral and ileac veins extending into the pelvis. Laboratory studies on admission prior to therapy show normal electrolytes, normal white blood cell (WBC) and platelet counts, normal prothrombin time, and an activated partial thromboplastin time 3× normal. Her pregnancy test is negative. Low-molecular-weight heparin therapy is initiated in the emergency department. Subsequent therapy should include:

A. Rituximab 375 mg/m^2 per week for 4 weeks
B. Warfarin with INR goal of 2.0–3.0 for 3 months
C. Warfarin with INR goal of 2.0–3.0 for 12 months
D. Warfarin with INR goal of 2.5–3.5 for life
E. Warfarin with an INR goal of 2.5–3.5 for 12 months followed by daily aspirin for life

13. Which of the following is the most frequent site of joint involvement in established rheumatoid arthritis (RA)?

A. Distal interphalangeal joint
B. Hip
C. Knee
D. Spine
E. Wrist

14. In patients with established rheumatoid arthritis, all of the following pulmonary radiographic findings may be explained by their rheumatologic condition EXCEPT:

14. (*Continued*)
A. Bilateral interstitial infiltrates
B. Bronchiectasis
C. Lobar infiltrate
D. Solitary pulmonary nodule
E. Unilateral pleural effusion

15. Which of the following is the earliest plain radiographic finding of rheumatoid arthritis?

A. Juxtaarticular osteopenia
B. No abnormality
C. Soft-tissue swelling
D. Subchondral erosions
E. Symmetric joint space loss

16. Which of the following statements regarding rheumatoid arthritis is true?

A. Africans and African Americans most commonly have the class II major histocompatibility complex allele HLA-DR4.
B. Females are affected three times more often than are males, and this difference is maintained throughout life.
C. The earliest lesion in rheumatoid arthritis is an increase in the number of synovial lining cells with microvascular injury.
D. There is an association with the class II major histocompatibility complex allele HLA-B27.
E. Titers of rheumatoid factor are not predictive of the severity of rheumatoid arthritis or its extraarticular manifestations.

17. A 46-year-old woman presents to your clinic with multiple complaints. She describes fatigue and general malaise over 2–3 months. Her appetite has decreased. She thinks she has unintentionally lost approximately 5.5 kg. Lately, she notes pain and stiffness in her fingers on both hands that is worse in the morning and with repetitive movement. She has a grandmother and a sister who have rheumatoid arthritis, and she is very concerned that she now has it as well. Which of her complaints represents the most common manifestation of established rheumatoid arthritis?

A. Fatigue and anorexia for more than 2 months with concomitant joint pain
B. Morning joint stiffness lasting for more than 1 hour
C. Pain in symmetric joints that is worsened with movement
D. Positive family history with two relatives with RA
E. Weight loss of more than 4.5 kg during period of active disease

18. All of the following are characteristic extraarticular manifestations of rheumatoid arthritis EXCEPT:

A. Anemia
B. Cutaneous vasculitis
C. Pericarditis
D. Secondary Sjögren's syndrome
E. Thrombocytopenia

19. All of the following agents have been shown to have disease-modifying antirheumatic drug (DMARD) efficacy in patients with rheumatoid arthritis EXCEPT:

A. Infliximab
B. Leflunomide
C. Methotrexate
D. Naproxen
E. Rituximab

20. Which of the following is the most common clinical presentation of acute rheumatic fever (ARF)?

A. Carditis
B. Chorea
C. Erythema marginatum
D. Polyarthritis
E. Subcutaneous nodules

21. A 19-year-old recent immigrant from Ethiopia comes to your clinic to establish primary care. She currently feels well. Her past medical history is notable for a recent admission to the hospital for new-onset atrial fibrillation. As a child in Ethiopia, she developed an illness that caused uncontrolled flailing of her limbs and tongue lasting approximately 1 month. She also has had three episodes of migratory large-joint arthritis during her adolescence that resolved with pills that she received from the pharmacy. She is currently taking metoprolol and warfarin and has no known drug allergies. Physical examination reveals an irregularly irregular heart beat with normal blood pressure. Her point of maximal impulse (PMI) is most prominent at the midclavicular line and is normal in size. An early diastolic rumble and a 3/6 holosystolic murmur are heard at the apex. A soft early diastolic murmur is also heard at the left third intercostal space. You refer her to a cardiologist for evaluation of valve replacement and echocardiography. What other intervention might you consider at this time?

A. Glucocorticoids
B. Daily aspirin

21. (*Continued*)
C. Daily doxycycline
D. Monthly penicillin G injections
E. Penicillin G injections as needed for all sore throats

22. A patient with a diagnosis of scleroderma who has diffuse cutaneous involvement presents with malignant hypertension, oliguria, edema, hemolytic anemia, and renal failure. You make a diagnosis of scleroderma renal crisis (SRC). What is the recommended treatment?

A. Captopril
B. Carvedilol
C. Clonidine
D. Diltiazem
E. Nitroprusside

23. A 57-year-old woman with depression and chronic migraine headaches reports several years of dry mouth and dry eyes. Her primary complaint is that she can no longer eat her favorite crackers, though she does report photosensitivity and eye burning on further questioning. She has no other associated symptoms. Examination shows dry, erythematous, sticky oral mucosa. All of the following tests are likely to be positive in this patient EXCEPT:

A. La/SS-B antibody
B. Ro/SS-A antibody
C. Schirmer's I test
D. Scl-70 antibody
E. Sialometry

24. Which of the following is the most common extraglandular manifestation of primary Sjögren's syndrome?

A. Arthralgias/arthritis
B. Lymphoma
C. Peripheral neuropathy
D. Raynaud's phenomenon
E. Vasculitis

25. A 44-year-old woman presents for evaluation of dry eyes and mouth. She first noticed these symptoms more than 5 years ago and the symptoms have worsened over time. She describes her eyes as gritty feeling, as if there were sand in her eyes. Sometimes her eyes burn, and she states that it is difficult to be outside in bright sunlight. In addition, her mouth is quite dry. In her job, she is frequently asked to give business presentations and finds it increasingly difficult to complete a 30- to 60-minute presentation.

25. (*Continued*)
She has water with her at all times. Although she reports good dental hygiene without any recent changes, her dentist has had to place fillings twice in the past 3 years for dental caries. Her only other past medical history is treated tuberculosis that she contracted while in the Peace Corps in Southeast Asia when in her 20s. She takes no medication regularly and does not smoke. Ocular examination reveals punctuate corneal ulcerations on Rose Bengal stain, and the Schirmer's test shows greater than 5 mm of wetness after 5 minutes. Her oral mucosa is dry with thick mucous secretions, and the parotid glands are enlarged bilaterally. Laboratory examination reveals positive antibodies to Ro and La (SS-A and SS-B). In addition, her chemistries reveal a sodium of 142 meq/L, potassium 2.6 meq/L, chloride 115 meq/L, and bicarbonate of 15 meq/L. What is the most likely cause of the hypokalemia and acidemia in this patient?

A. Diarrhea
B. Distal (type I) renal tubular acidosis
C. Hypoaldosteronism
D. Purging with underlying anorexia nervosa
E. Renal compensation for chronic respiratory alkalosis

26. A patient with primary Sjögren's syndrome that was diagnosed 6 years ago and treated with tear replacement for symptomatic relief notes continued parotid swelling for the last 3 months. She has also noted enlarging posterior cervical lymph nodes. Evaluation shows leukopenia and low C4 complement levels. What is the most likely diagnosis?

A. Amyloidosis
B. Chronic pancreatitis
C. HIV infection
D. Lymphoma
E. Secondary Sjögren's syndrome

27. The histocompatibility antigen HLA-B27 is present in what percentage of patients with ankylosing spondylitis?

A. 10%
B. 30%
C. 50%
D. 90%
E. 100%

28. Which of the following is the most common extraarticular manifestation of ankylosing spondylitis?

A. Anterior uveitis
B. Aortic insufficiency

28. (*Continued*)
C. Inflammatory bowel disease
D. Pulmonary fibrosis
E. Third-degree heart block

29. A 25-year-old man sees his primary care physician for evaluation of low back pain. The pain is severe, is worse in the morning, and is relieved with exercise and is worse with rest; in particular, nighttime sleeping is difficult. He does feel quite stiff in the morning for at least 30 minutes. An MRI of his lower back is obtained and shows active inflammation in the sacroiliac joint. On further questioning, he reports a history of unilateral eye redness treated with corticosteroids about 2 years ago. A test for HLA-B27 is positive. Which of the following is first-line therapy for his condition?

A. Infliximab
B. Naproxen
C. Prednisone
D. Rituximab
E. Tramadol

30. A 27-year-old man is seen at his primary care physician's office for evaluation of painful arthritis involving the right knee that is associated with finger welling diffusely. He is otherwise healthy, but does recall a severe bout of diarrheal illness about 3–4 weeks prior that spontaneously resolved. He takes no medications and reports rare marijuana use. On review of systems, he reports painful urination. Examination shows inflammatory arthritis of the right knee, dactylitis, and normal genitourinary examination. He is diagnosed with reactive arthritis. Which of the following is the most likely etiologic agent of his diarrhea?

A. *Campylobacter jejuni*
B. *Clostridium difficile*
C. *Escherichia coli*
D. *Helicobacter pylori*
E. *Shigella flexneri*

31. A 28-year-old woman undergoes evaluation for weight loss and bloody diarrhea that is ultimately diagnosed as Crohn's disease. She has been diagnosed with dactylitis and bilateral sacroiliitis within the past 6 months. She is scheduled to begin treatment with infliximab in 2 weeks for her Crohn's disease. Which of the following statements is true regarding the effect of infliximab on her arthritis?

A. Although infliximab is likely to improve her arthritic symptoms, NSAIDs should be tried first.
B. Although infliximab is very effective therapy for Crohn's disease, it will have no effect on her arthritis.

31. (*Continued*)

C. Her arthritis is unrelated to Crohn's disease, and because of this she should undergo a thorough evaluation for infectious causes before undergoing immunosuppressive therapy.
D. Infliximab is very effective therapy for this type of arthritis.
E. None of the above.

32. Which of the following statements regarding the arthritis of Whipple's disease is true?

A. Arthritis is a rare finding in Whipple's disease.
B. Joint manifestations are usually concurrent with gastrointestinal symptoms and malabsorption.
C. Radiography frequently shows joint erosions.
D. Synovial fluid examination is unlikely to show polymorphonuclear cells.
E. None of the above.

33. A 35-year-old man has severe ankylosing spondylitis that is unresponsive to NSAID therapy. Therapy with infliximab has been recommended and he is wondering about potential side effects. All of the following are common potential side effects from this medication EXCEPT:

A. Demyelinating disorders
B. Disseminated tuberculosis
C. Exacerbation of congestive heart failure
D. Hypersensitivity pneumonitis
E. Pancytopenia

34. Which of the following definitions best fits the term enthesitis?

A. Alteration of joint alignment so that articulating surfaces incompletely approximate each other
B. Inflammation at the site of tendinous or ligamentous insertion into bone
C. Inflammation of the periarticular membrane lining the joint capsule
D. Inflammation of a saclike cavity near a joint that decreases friction
E. A palpable vibratory or crackling sensation elicited with joint motion

35. A 35-year-old female presents to her primary care doctor complaining of diffuse body and joint pain. When asked to describe which of her joints are most affected, she answers, "All of them." There is no associated stiffness, redness, or swelling of the joints. No Raynaud's phenomenon has been appreciated. Occasionally she notes numbness in the fingers and toes. The patient complains of chronic pain and poor sleep quality that she feels is due to her pain. She previously

35. (*Continued*)

was seen in the clinic for chronic headaches that were felt to be tension related. She has tried taking over-the-counter ibuprofen twice daily without relief of pain. She has no other medical problems. On physical examination, the patient appears comfortable. Her joints exhibit full range of motion without evidence of inflammatory arthritis. She does have pain with palpation at bilateral suboccipital muscle insertions, at C5, at the lateral epicondyle, in the upper outer quadrant of the buttock, at the medial fat pad of the knee proximal to the joint line, and unilaterally on the second right rib. The erythrocyte sedimentation rate is 12 seconds. Antinuclear antibodies are positive at a titer of 1:40 in a speckled pattern. The patient is HLA-B27 positive. Rheumatoid factor is negative. Radiograms of the cervical spine, hips, and elbows are normal. What is the most likely diagnosis?

A. Ankylosing spondylitis
B. Disseminated gonococcal infection
C. Fibromyalgia
D. Rheumatoid arthritis
E. Systemic lupus erythematosus

36. A 42-year-old male presents with complaints of a rash and joint pain. He first noticed the rash 6 months ago. It is primarily on the hands **(Figure 36)**, the extensor surfaces of the elbows, and the knees, low back, and scalp. Although he complains of the appearance of these lesions, they do not itch or hurt. He has not been previously evaluated for them and has recently noticed changes in the nail beds. For the last 2 weeks, the patient has had increasingly severe pain in the distal joints of the hands and feet. His hands are so painful that he is having trouble writing and holding utensils. He denies fevers, weight loss, fatigue, cough, shortness of breath, or changes in bowel or bladder habits. Which of the following is the most likely diagnosis?



FIGURE 36

36. (*Continued*)

A. Arthritis associated with inflammatory bowel disease
B. Gout
C. Osteoarthritis
D. Psoriatic arthritis
E. Rheumatoid arthritis

37. All of the following vasculitic syndromes are thought to be due to immune complex deposition EXCEPT:

A. Cryoglobulinemic vasculitis
B. IgA vasculitis (Henoch-Schönlein)
C. Polyarteritis nodosa associated with hepatitis B
D. Serum sickness
E. Granulomatosis with polyangiitis (Wegener's)

38. A 53-year-old man presents with a vasculitis syndrome with features that include a nasal septal perforation, glomerulonephritis, and a normal eosinophil count. His cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) is positive. Which of the following syndromes is he most likely to have?

A. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
B. IgA vasculitis (Henoch-Schönlein)
C. Microscopic polyangiitis
D. Ulcerative colitis
E. Granulomatosis with polyangiitis (Wegener's)

39. A 40-year-old male presents to the emergency department with 2 days of low-volume hemoptysis. He reports that he has been coughing up 2–5 tablespoons of blood each day. He reports mild chest pain, low-grade fevers, and weight loss. In addition, he has had about 1 year of severe upper respiratory symptoms including frequent epistaxis and purulent discharge treated with several courses of antibiotics. Aside from mild hyperlipidemia, he is otherwise healthy. His only medications are daily aspirin and lovastatin. On physical examination he has normal vital signs, and the upper airway is notable for saddle nose deformity and clear lungs. A CT of the chest shows multiple cavitating nodules, and urinalysis shows red blood cells. Which of the following tests offers the highest diagnostic yield to make the appropriate diagnosis?

A. Deep skin biopsy
B. Percutaneous kidney biopsy
C. Pulmonary angiogram
D. Surgical lung biopsy
E. Upper airway biopsy

40. An 84-year-old woman sees her primary care physician for evaluation of severe headaches. She noted these several weeks ago and they have been getting worse. Although she has not had any visual aura, she is concerned that she has been intermittently losing vision in her left eye for the last few days. She denies new weakness or numbness, but she does report jaw pain with eating. Her past medical history includes coronary artery disease requiring a bypass grafting 10 years prior, diabetes mellitus, hyperlipidemia, and mild depression. Full review of symptoms is notable for night sweats and mild low back pain that is particularly prominent in the morning. Which of the following is the next most appropriate step?

A. Aspirin 975 mg po daily
B. Measurement of erythrocyte sedimentation rate
C. Prednisone 60 mg daily
D. Referral for temporal artery biopsy
E. Referral for ultrasound of temporal artery

41. A 54-year-old man is evaluated for cutaneous vasculitis and peripheral nephropathy. Because of concomitant renal dysfunction he undergoes kidney biopsy that shows glomerulonephritis. Cryoglobulins are demonstrated in the peripheral blood. Which of the following laboratory studies should be sent to determine the etiology?

A. Hepatitis B surface antigen
B. Cytoplasmic ANCA
C. Hepatitis C polymerase chain reaction (PCR)
D. HIV antibody
E. Rheumatoid factor

42. A 54-year-old man is admitted for persistent lower abdominal and groin pain that began 7 months previously. Two months before his present admission, he required exploratory laparoscopy for acute abdominal pain and presumed cholecystitis. This revealed necrotic omental tissue and pericholecystitis necessitating omentectomy and cholecystectomy. However, the pain continued unchanged. He currently describes it as periumbilical and radiating into his groin and legs. It becomes worse with eating. The patient has also had episodic severe testicular pain, bowel urgency, nausea, vomiting, and diuresis. He has lost approximately 22.7 kg over the preceding 6 months. His past medical history is significant for hypertension that has recently become difficult to control.

Medications on admission include aspirin, hydrochlorothiazide, hydromorphone, lansoprazole, metoprolol, and quinapril. On physical examination, the patient appears comfortable. His blood pressure is

42. (*Continued*)
170/100 mmHg, his heart rate is 88 beats/min, and he is afebrile. He has normal first and second heart sounds without murmurs, and an S4 is present. There are no carotid, renal, abdominal, or femoral bruits.

His lungs are clear to auscultation. Bowel sounds are normal. Abdominal palpation demonstrates minimal diffuse tenderness without rebound or guarding. No masses are present, and the stool is negative for occult blood. During the examination, the patient develops Raynaud's phenomenon in his right hand that persists for several minutes. His neurologic examination is intact. Admission laboratory studies reveal an erythrocyte sedimentation rate of 72 mm/h, a BUN of 17 mg/dL, and a creatinine of 0.8 mg/dL. The patient has no proteinuria or hematuria. Tests for antinuclear antibodies, anti–double-stranded-DNA antibodies, and antineutrophil cytoplasmic antibodies are negative. Liver function tests are abnormal with an AST of 89 IU/L and an ALT of 112 IU/L. Hepatitis B surface antigen and e antigen are positive. Mesenteric angiography demonstrates small, beaded aneurysms of the superior and inferior mesenteric veins. What is the most likely diagnosis?

A. Hepatocellular carcinoma
B. Ischemic colitis
C. Microscopic polyangiitis
D. Mixed cryoglobulinemia
E. Polyarteritis nodosa

43. An 18-year-old man is admitted to the hospital with acute onset of crushing substernal chest pain that began abruptly 30 minutes ago. He reports the pain radiating to his neck and right arm. He has otherwise been in good health. He currently plays trumpet in his high school marching band but does not participate regularly in aerobic activities. On physical examination, he is diaphoretic and tachypneic. His blood pressure is 100/48 mmHg and heart rate is 110 beats/min. His cardiovascular examination shows a regular rhythm but is tachycardic. A II/VI holosystolic murmur is heard best at the apex and radiates to the axilla. His lungs have bilateral rales at the bases. The electrocardiogram demonstrates 4 mm of ST elevation in the anterior leads. On further questioning regarding his past medical history, he recalls having been told that he was hospitalized for some problem with his heart when he was 2 years old. His mother, who accompanies him, reports that he received aspirin and γ-globulin as treatment. Since that time, he has required intermittent follow-up with echocardiography. What is the most likely cause of this patient's acute coronary syndrome?

43. (*Continued*)
A. Dissection of the aortic root and left coronary ostia
B. Presence of a myocardial bridge overlying the left anterior descending artery
C. Thrombosis of a coronary artery aneurysm
D. Vasospasm following cocaine ingestion
E. Vasculitis involving the left anterior descending artery

44. Which of the following is required for the diagnosis of Behçet's disease?

A. Large-vessel vasculitis
B. Pathergy test
C. Recurrent oral ulceration
D. Recurrent genital ulceration
E. Uveitis

45. A 25-year-old female presents with a complaint of painful mouth ulcerations. She describes these lesions as shallow ulcers that last for 1–2 weeks. The ulcers have been appearing for the last 6 months. For the last 2 days, the patient has had a painful red eye. She has had no genital ulcerations, arthritis, skin rashes, or photosensitivity. On physical examination, the patient appears well developed and in no distress. She has a temperature of 37.6°C (99.7°F), heart rate of 86 beats/min, blood pressure of 126/72 mmHg, and respiratory rate of 16 breaths/min. Examination of the oral mucosa reveals two shallow ulcers with a yellow base on the buccal mucosa. The ophthalmologic examination is consistent with anterior uveitis. The cardiopulmonary examination is normal. She has no arthritis, but medially on the right thigh there is a palpable cord in the saphenous vein. Laboratory studies reveal an erythrocyte sedimentation rate of 68 seconds. White blood cell count is 10,230/μL with a differential of 68% polymorphonuclear cells, 28% lymphocytes, and 4% monocytes. The antinuclear antibody and anti-dsDNA antibody are negative. C3 is 89 mg/dL, and C4 is 24 mg/dL. What is the most likely diagnosis?

A. Behçet's syndrome
B. Cicatricial pemphigoid
C. Discoid lupus erythematosus
D. Sjögren's syndrome
E. Systemic lupus erythematosus

46. What is the best initial treatment for the patient in question 45?

A. Colchicine
B. Intralesional interferon α

46. (*Continued*)
C. Systemic glucocorticoids and azathioprine
D. Thalidomide
E. Topical glucocorticoids including ophthalmic prednisolone

47. Relapsing polychondritis may be a primary disease or may be associated with other rheumatologic diseases. All of the following conditions are associated with relapsing polychondritis EXCEPT:

A. Myelodysplastic syndrome
B. Primary biliary cirrhosis
C. Scleroderma
D. Spondyloarthritides
E. Systemic lupus erythematosus

48. A 47-year-old man is evaluated for 1 year of recurrent episodes of bilateral ear swelling. The ear is painful during these events, and the right ear has become floppy. He is otherwise healthy and reports no illicit habits. He works in an office and his only sport is tennis. On examination, the left ear has a beefy red color, and the pinna is tender and swollen; the earlobe appears minimally swollen but is neither red nor tender. Which of the following is the most likely explanation for this finding?

A. Behçet's syndrome
B. Cogan's syndrome
C. Hemoglobinopathy
D. Recurrent trauma
E. Relapsing polychondritis

49. A 25-year-old African-American woman is evaluated for bilateral hilar lymphadenopathy found on a routine chest radiograph performed before a laparoscopic cholecystectomy. She undergoes mediastinoscopy, and multiple noncaseating granulomas are identified in her lymph nodes. All of the following may explain this finding EXCEPT:

A. Alveolar proteinosis
B. Atypical mycobacteria
C. Beryllium exposure
D. Histoplasmosis
E. Malignancy
F. Sarcoidosis

50. A 34-year-old woman has a history of cutaneous sarcoidosis that has been managed with hydroxychloroquine for the last 5 years. After an episode of right flank pain and hematuria, she is diagnosed with renal calculus. Which of the following statements regarding her renal calculus is true?

50. (*Continued*)
A. Exogenous vitamin D and sunlight exposure in patients with sarcoidosis may exacerbate hypercalcemia and associated renal calculus.
B. Hypercalcemia is rare in sarcoidosis and is unlikely to contribute to the patient's calculus.
C. Hypercalcemia in sarcoidosis occurs through increased production of 25-dihydroxyvitamin D by the skin.
D. If she is to begin therapy with oral calcium to treat the renal stone, a 24-hour urine phosphate should be obtained before and after initiation of therapy.
E. None of the above.

51. All of the following agents have been shown to improve symptoms or function in patients with sarcoidosis EXCEPT:

A. Etanercept
B. Hydroxychloroquine
C. Infliximab
D. Methotrexate
E. Prednisone

52. All of the following statements regarding the clinical manifestations of sarcoidosis are true EXCEPT:

A. Cardiac involvement occurs in 25% of patients.
B. Eye involvement is typically anterior uveitis.
C. Liver involvement is typically manifest by elevation of alkaline phosphatase.
D. Lung involvement occurs in over 90% of cases.
E. Skin involvement occurs in approximately one-third of patients.

53. You are seeing a 56-year-old woman for complaints of joint pain and stiffness. All of the following signs or symptoms would be indicative of inflammatory causes of arthritis EXCEPT:

A. Elevations in erythrocyte sedimentation rate
B. Fatigue, fever, or weight loss
C. Persistence for longer than 6 weeks
D. Presence of soft-tissue swelling around affected joints
E. Prolonged morning stiffness

54. A 22-year-old man is seen for a shoulder injury that occurred while pitching in a baseball game. He describes feeling a snap then acute pain in the shoulder of his left arm while throwing the ball. Which of the following findings would be most concerning for a tear of one of the rotator cuff muscles?

A. Inability to hold the arm at 90° following passive abduction

54. (*Continued*)

B. Inability to actively raise the arm more than 90° with forward flexion
C. Pain with palpation over the bicipital groove while rotating the arm internally and externally
D. Pain with palpation while applying pressure anteriorly along the joint and rotating the arm internally and externally
E. Pain with passive abduction of the arm

55. A 62-year-old white male presents with a chief complaint of right knee pain and swelling. Past medical history is significant for obesity with a body mass index (BMI) of 34 kg/m^2, diet-controlled type 2 diabetes mellitus, and hypertension. His medications include hydrochlorothiazide and acetaminophen as needed for pain. Physical examination is remarkable for a moderately sized effusion of the right knee, with range of motion limited to 90° of flexion and 160° of extension. There is minimal warmth and no redness. He has crepitus with range of motion. With weight bearing, he has outward bowing of the legs bilaterally. A radiogram of the right knee shows osteophytes and joint space narrowing. Which of the following is the most likely finding on joint fluid examination?

A. A Gram stain showing gram-positive cocci in clusters
B. A white blood cell count of 1110/μL
C. A white blood cell count of 22,000/
D. Positively birefringent crystals on polarizing light microscopy
E. Negatively birefringent crystals on polarizing light microscopy

56. A 32-year-old woman presents to the clinic with right thumb and wrist pain that has worsened over several weeks. She has pain when she pinches her thumb against her other fingers. Her only other history is that she is a new mother with an 8-week-old infant at home. On physical examination she has mild swelling and tenderness over the radial styloid process, and pain is elicited when she places her thumb in her palm and grasps it with her fingers. A Phalen maneuver is negative. Which condition is most likely?

A. Carpal tunnel syndrome
B. De Quervain's tenosynovitis
C. Gouty arthritis of the first metacarpophalangeal joint
D. Palmar fasciitis
E. Rheumatoid arthritis

57. A 62-year-old woman presents complaining of hand pain bilaterally that has been gradually progressive over the past year. She has previously worked as

57. (*Continued*)

a seamstress in a factory making gloves for more than 35 years. You suspect osteoarthritis. All of the following factors on history or physical examination are characteristic of this diagnosis EXCEPT:

A. Evidence of bilateral swelling and warmth affecting the wrists only
B. Joint space narrowing and osteophytes at the proximal and distal interphalangeal joints on x-ray
C. Pain that becomes worse when preparing meals
D. Presence of Heberden's nodes
E. Stiffness that is worse after brief periods of rest with occasional locking of the more affecting joints

58. A 73-year-old woman with a medical history of obesity and diabetes mellitus presents to your clinic complaining of right knee pain that has been progressive and is worse with walking or standing. She has taken over-the-counter nonsteroidal anti-inflammatory drugs without relief. She wants to know what is wrong with her knee and what may have caused it. X-rays are performed and reveal cartilage loss and osteophyte formation. Which of the following represents the most potent risk factor for the development of osteoarthritis?

A. Age
B. Gender
C. Genetic susceptibility
D. Obesity
E. Previous joint injury

59. A 53-year-old man presents to your clinic complaining of bilateral knee pain. He states that the pain worsens with walking and is not present at rest. He has been experiencing knee pain intermittently for many months and has had no relief from over-the-counter analgesics. He has a history of hypertension and obesity. When he was in high school and college, he played football and basketball. Which of the following represents the best initial treatment strategy for this patient?

A. Avoidance of walking for several weeks
B. Light daily walking exercises
C. Low-dose, long-acting narcotics
D. Oral steroid pulse
E. Weight loss

60. A 74-year-old man is seen by his primary care provider 6 weeks following an acute gout attack. He has a prior history of gout presenting similarly on two prior occasions within the past 6 months. His past

60. (*Continued*)
medical history is significant for congestive heart failure, hypercholesterolemia, and stage III chronic kidney disease. He is taking pravastatin, aspirin, furosemide, metolazone, lisinopril, and metoprolol XL. His glomerular filtration rate is 38 mL/min, creatinine is 2.2 mg/dL, and uric acid level is 9.3 mg/dL. He is wondering if there is any therapy that might lessen his likelihood of repeated gout attacks. Which of the following medication regimens is most appropriate for the treatment of this patient?

A. Allopurinol 800 mg daily
B. Colchicine 0.6 mg bid
C. Febuxostat 40 mg daily
D. Indomethacin 25 mg twice daily
E. Probenecid 250 mg twice daily

61. A 64-year-old man with congestive heart failure presents to the emergency department complaining of acute onset of severe pain in his right foot. The pain began during the night and awoke him from a deep sleep. He reports the pain to be so severe that he could not wear a shoe or sock to the hospital. His current medications are furosemide 40 mg twice daily, carvedilol 6.25 mg twice daily, candesartan 8 mg once daily, and aspirin 325 mg once daily. On examination, he is febrile to 38.5°C (101.3°F). The first toe of the right foot is erythematous and exquisitely tender to touch. There is significant swelling and effusion of the first metatarsophalangeal joint on the right foot. No other joints are affected. Which of the following findings would be expected on arthrocentesis?

A. Glucose level of less than 25 mg/dL
B. Positive Gram stain
C. Presence of strongly negatively birefringent needle-shaped crystals under polarized light microscopy
D. Presence of weakly positively birefringent rhomboidal crystals under polarized light microscopy
E. White blood cell (WBC) count greater than 100,000/μL

62. A 24-year-old woman is admitted to the hospital with symptoms of fever and a swollen, painful right knee. About 3 weeks prior to the current syndrome, the patient had systemic symptoms including fevers, chills, and migratory joint pains affecting the hands, wrists, knees, hips, and ankles. At that time, she noticed a few small papules on her upper chest and hands. These have subsequently resolved. She has no significant past medical history. She currently works as a landscape designer and does not recall

62. (*Continued*)
any recent tick or insect bites. Her only medication is an oral contraceptive. She is unmarried and has multiple sexual partners. On physical examination, the patient has a temperature of 38.4°C (101.2°F), heart rate of 124 beats/min, respiratory rate of 24 breaths/min, and blood pressure of 102/68 mmHg. Her right knee demonstrates redness, warmth, swelling, and pain with movement. An arthrocentesis demonstrates a white blood cell count of 66,000/μL (90% neutrophils). No crystals or organisms are seen. Which of the following would be most likely to yield the correct diagnosis?

A. Bacterial cultures of the cervix
B. Bacterial cultures of the synovial fluid
C. Blood cultures
D. IgG directed against *Borrelia burgdorferi*
E. Rheumatoid factor

63. A 66-year-old woman with a history of rheumatoid arthritis and frequent attacks of pseudogout in her left knee presents with night sweats and a 2-day history of left knee pain. Her medications include methotrexate 15 mg weekly, folate 1 mg daily, prednisone 5 mg daily, and ibuprofen 800 mg three times daily as needed for pain. On physical examination, her temperature is 38.6°C (101.5°F), heart rate is 110 beats/min, blood pressure is 104/78 mmHg, and oxygen saturation is 97% on room air. Her left knee is swollen, red, painful, and warm. With 5° of flexion or extension, she develops extreme pain. She has evidence of chronic joint deformity in her hands, knees, and spine. Peripheral white blood cell (WBC) count is 16,700 cells/μL with 95% neutrophils. A diagnostic tap of her left knee reveals 168,300 WBCs per and 99% neutrophils, and diffuse needle-shaped birefringent crystals are present. Gram stain shows rare gram-positive cocci in clusters. Management includes all of the following EXCEPT:

A. Blood cultures
B. Glucocorticoids
C. Needle aspiration of joint fluid
D. Orthopedic surgery consult
E. Vancomycin

64. A 42-year-old woman is seen in her primary care doctor's office complaining of diffuse pains and fatigue. She has a difficult time localizing the pain to any particular joint or location, but reports that it affects her upper and lower extremities, neck, and hips. It is described as achy and 10 out of 10 in intensity. She feels that her joints are stiff, but does not

64. (*Continued*)
notice that it is worse in the morning. The pain has been present for the past 6 months and is increasing in intensity. She has tried both over-the-counter ibuprofen and acetaminophen without significant relief. The patient feels as if the pain is interfering with her ability to get restful sleep and is making it difficult for her to concentrate. She has missed multiple days of work as a waitress and fears that she will lose her job. There is a medical history of depression and obesity. The patient currently is taking venlafaxine sustained release 150 mg daily. She has a family history of rheumatoid arthritis in her mother. She smokes 1 pack of cigarettes daily. On physical examination vital signs are normal. Body mass index is 36 kg/m^2. Joint examination demonstrates no erythema, swelling, or effusions. There is diffuse pain with palpation at the insertion points of the suboccipital muscles, at the midpoint of the upper border of the trapezius muscle, along the second costochondral junction, at the lateral epicondyles, and along the medial fat pad of the knees. All of the following statements regarding the cause of this patient's diffuse pain syndrome are true EXCEPT:

A. Cognitive dysfunction, sleep disturbance, anxiety, and depression are common comorbid neuropsychological conditions.
B. Pain in this syndrome is associated with increased evoked pain sensitivity.
C. Pain in this syndrome is often localized to specific joints.
D. This syndrome is present in 2–5% of the general population, but increases in prevalence to 20% or more of patients with degenerative or inflammatory rheumatic disorders.
E. Women are nine times more likely than men to be affected by this syndrome.

65. A 36-year-old woman presents to your office with diffuse pain throughout her body associated with fatigue, insomnia, and difficulty concentrating. She finds the pain difficult to localize, but reports that it is 7–8 out of 10 in intensity and is not relieved by nonsteroidal anti-inflammatory medications. She has a long-standing history of generalized anxiety disorder and is treated with sertraline 100 mg daily as well as clonazepam 1 mg twice daily. On examination, she has pain with palpation at several musculoskeletal sites. Her laboratory examination demonstrates a normal complete blood count, basic metabolic panel, erythrocyte sedimentation rate, and rheumatoid factor. You diagnose her with fibromyalgia. All of the following therapies are recommended as part of the treatment plan for fibromyalgia EXCEPT:

65. (*Continued*)
A. An exercise program that includes strength training, aerobic exercise, and yoga
B. Cognitive-behavioral therapy for insomnia
C. Milnacipran
D. Oxycodone
E. Pregabalin

66. A 53-year-old woman presents to your clinic complaining of fatigue and generalized pain that have worsened over 2 years. She also describes irritability and poor sleep, and is concerned that she is depressed. She reveals that she was recently separated from her husband and has been stressed at work. Which of the following elements in her history and physical examination would meet American College of Rheumatology criteria for diagnosis of fibromyalgia?

A. Diffuse chronic pain and abnormal sleep
B. Diffuse pain without other etiology and evidence of major depression
C. Major depression, life stressor, chronic pain, and female gender
D. Major depression and pain on palpation at 6 of 18 tender point sites
E. Widespread chronic pain and pain on palpation at 11 of 18 tender point sites

67. A 42-year-old man is found to have the following finding on a physical examination **(Figure 67)**. All of the following conditions are associated with this finding EXCEPT:



FIGURE 67
(Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, Copyright 1991, 1995. Used by permission of the American College of Rheumatology.)

A. Chronic obstructive pulmonary disease
B. Cyanotic congenital heart disease
C. Cystic fibrosis
D. Hepatocellular carcinoma
E. Hyperthyroidism

68. A 64-year-old woman sees her primary care physician complaining of hip pain for about 1 week. She localizes the pain to the lateral aspect of her right hip and describes it as sharp. It is worse with movement, and she finds it difficult to lie on her right side. The pain began soon after the patient planted her garden. She has a medical history of obesity, osteoarthritis of the knees, and hypertension. Her medications include losartan 50 mg daily and hydrochlorothiazide 25 mg daily. For the pain, she has taken ibuprofen 600 mg as needed with mild to moderate relief of pain. On physical examination, the patient is not febrile and her vital signs are unremarkable. On examination of the hip, pain is elicited with external rotation and resisted abduction of the hip. Direct palpation over the lateral aspect of the upper portion of the femur near the hip joint reproduces the pain. What is the most likely diagnosis in this patient?

A. Avascular necrosis of the hip
B. Iliotibial band syndrome
C. Meralgia paresthetica
D. Septic arthritis
E. Trochanteric bursitis

69. A 32-year-old woman is seen in the clinic with a complaint of left knee pain. She enjoys running long distances and is currently training for a marathon. She is running on average 30–40 miles weekly. She currently is experiencing an aching pain on the lateral aspect of her left knee. There is a burning sensation that also continues up the lateral aspect of her thigh. She denies any injury to her knee, and she has not felt that it was hot or swollen. She is otherwise healthy and takes no medications other than herbal supplements. Physical examination of the knee reveals point tenderness over the lateral femoral condyle that is worse with flexing the knee. The patient is asked to lie on her right side with her right knee and hip flexed at 90°. Her left leg is extended at the hip and slowly lowered into adduction behind the bottom leg, reproducing the patient's left knee pain. All of the following treatments can be recommended for this patient EXCEPT:

A. Assessment of the patient's running shoes to ensure a proper fit
B. Glucocorticoid injection so as not to interfere with the patient's continued preparation for the upcoming marathon
C. Ibuprofen 600–800 mg every 6 hours as needed for pain
D. Referral for physical therapy
E. Referral for surgical release if conservative therapy fails

70. A 58-year-old female presents complaining of right shoulder pain. She does not recall any prior injury but notes that the shoulder has been getting progressively stiffer over the last several months. She previously had several episodes of bursitis of the right shoulder that were treated successfully with NSAIDs and steroid injections. The patient's past medical history is also significant for diabetes mellitus, for which she takes metformin and glyburide. On physical examination, the right shoulder is not warm or red but is tender to touch. Passive and active range of motion is limited in flexion, extension, and abduction. A right shoulder radiogram shows osteopenia without evidence of joint erosion or osteophytes. What is the most likely diagnosis?

A. Adhesive capsulitis
B. Avascular necrosis
C. Bicipital tendinitis
D. Osteoarthritis
E. Rotator cuff tear

71. A 64-year-old African American man is evaluated in the hospital for congestive heart failure, renal failure, and polyneuropathy. Physical examination on admission was notable for these findings and raised waxy papules in the axilla and inguinal region. Admission laboratories showed a blood urea nitrogen of 90 mg/dL and a creatinine of 6.3 mg/dL. Total protein was 9.0 g/dL with an albumin of 3.2 g/dL. Hematocrit was 24%, and white blood cell and platelet counts were normal. Urinalysis was remarkable for 3+ proteinuria but no cellular casts. Further evaluation included an echocardiogram with a thickened left ventricle and preserved systolic function. Which of the following tests is most likely to diagnose the underlying condition?

A. Bone marrow biopsy
B. Electromyogram (EMG) with nerve conduction studies
C. Fat pad biopsy
D. Right heart catheterization
E. Renal ultrasonography

72. An elevation in which of the following serum enzymes is the most *sensitive* indicator of myositis?

A. Aldolase
B. Creatinine kinase
C. Glutamic-oxaloacetic transaminase
D. Glutamate pyruvate transaminase
E. Lactate dehydrogenase

73. A 64-year-old woman is evaluated for weakness. For several weeks she has had difficulty brushing her teeth and combing her hair. She has also noted a rash on her face. Examination is notable for a heliotrope rash and proximal muscle weakness. Serum creatine kinase (CK) is elevated and she is diagnosed with dermatomyositis. After evaluation by a rheumatologist, she is found to have anti-Jo-1 antibodies. She is also likely to have which of the following findings?

A. Ankylosing spondylitis
B. Inflammatory bowel disease
C. Interstitial lung disease
D. Primary biliary cirrhosis
E. Psoriasis

74. A 63-year-old woman is evaluated for a rash on her eyes and fatigue for 1 month. She reports difficulty with arm and leg strength and constant fatigue, but no fevers or sweats. She also notes that she has a red discoloration around her eyes. She has hypothyroidism but is otherwise well. On examination she has a heliotrope rash and proximal muscle weakness. A diagnosis of dermatomyositis is made after demonstration of elevated serum creatinine kinase and confirmatory EMGs. Which of the following studies

74. (*Continued*)
should be performed as well to look for associated conditions?

A. Mammogram
B. Serum antinuclear antibody measurement
C. Stool examination for ova and parasites
D. Thyroid-stimulating immunoglobulins
E. Titers of antibodies to varicella zoster

75. You are seeing your patient with polymyositis for follow-up. He has been taking prednisone at high doses for 2 months, and you initiated mycophenolate mofetil at the last clinic visit for a steroid-sparing effect. He began a steroid taper 2 weeks ago. His symptoms were predominantly in the lower extremities and face, and he has improved considerably. He no longer needs a cane and his voice has returned to normal. Laboratory data show a creatine kinase (CK) of 1300 U/L, which is unchanged from 2 months ago. What is the most appropriate next step in this patient's management?

A. Continue current management.
B. Continue high-dose steroids with no taper.
C. Switch mycophenolate to methotrexate.
D. Repeat muscle biopsy.

ANSWERS

1. The answer is A.
(Chap. 1) The innate immune system is phylogenetically the oldest form of immunologic defense system, inherited from invertebrates. This defense system uses germ line–encoded proteins to recognize pathogen-associated molecular patterns. Cells of the innate immune system include macrophages, dendritic cells, and natural killer lymphocytes. The critical components of the innate immune system include recognition by germ line–encoded host molecules, recognition of key microbe virulence factors but not recognition of self molecules, and nonrecognition of benign foreign molecules or microbes. Adaptive immunity is found only in vertebrate animals and is based on the generation of antigen receptors on T and B lymphocytes by gene rearrangements, such that individual T or B cells express unique antigen receptors on their surface capable of recognizing diverse environmental antigens.

2. The answer is A.
(Chap. 1) Complement activity, which results from the sequential interaction of a large number of plasma and cell membrane proteins, plays an important role in the inflammatory response. The classic pathway of complement activation is initiated by an antibody–antigen interaction. The first complement component (C1, a complex composed of three proteins) binds to immune complexes with activation mediated by C1q. Active C1 then initiates the cleavage and concomitant activation of components C4 and C2. The activated C1 is destroyed by a plasma protease inhibitor termed C1 esterase inhibitor. This molecule also regulates clotting factor XI and kallikrein. Patients with a deficiency of C1 esterase inhibitor may develop angioedema, sometimes leading to death by asphyxia. Attacks may be precipitated by stress or trauma. In addition to low antigenic or functional levels of C1 esterase inhibitor, patients with this autosomal-dominant condition may have normal levels of C1 and C3 but low levels of C4 and C2. Danazol therapy produces a striking increase in the level of this important inhibitor and alleviates the symptoms in many patients. An acquired form of angioedema caused by a deficiency of C1 esterase inhibitor has been described in patients with autoimmune or malignant disease.

3. The answer is C.

(Chap. 2) The human major histocompatibility complex genes are located on a 4-megabase region on chromosome 6. The major function of the MHC complex genes is to produce proteins that are important in developing immunologic specificity through their role in binding antigen for presentation to T cells. This process is nonspecific, and the ability of an HLA molecule to bind to a particular protein depends on the molecular fit between the amino acid sequence of a particular protein and the corresponding domain on the MHC molecule. Once a peptide has bound, the MHC-peptide complex binds to the T-cell receptor, after which the T cell must determine if an immune response should be generated. If an antigen is similar to an endogenous protein, the potential antigen will be recognized as a self-peptide and tolerance to the antigen will be continued. The MHC I and II complexes have been implicated in the development of many autoimmune diseases, which occur when T cells fail to recognize a peptide as a self-peptide and an immune response is allowed to develop. MHC I and II genes also play a major role in tissue compatibility for transplantation and are important in generating immune-mediated rejection. The other answers listed refer to functions of immunoglobulins. The variable region of the immunoglobulin is a B cell–specific response to an antigen to promote neutralization of the antigen through agglutination and precipitation. The constant region of the immunoglobulin is able to nonspecifically activate the immune system through complement activation and promotion of phagocytosis by neutrophils and macrophages.

4. The answer is A.

(Chap. 4) Antinuclear antibodies are nearly ubiquitous in patients with systemic lupus erythematosus, with demonstration in 90% of affected patients. There are many other antibodies that can be demonstrated. The next most common antibodies are anti-dsDNA and anti-histone. Anti-dsDNA is very specific to SLE and may correlate with disease activity, nephritis, and vasculitis. Antihistone is more frequent in drug-induced SLE. Antiphospholipid antibodies can be demonstrated in about half of affected patients, while the remainder is present in less than half of SLE cases.

5. The answer is B.

(Chap. 4) There are published criteria for systemic lupus erythematosus. They include four or more of the following criteria from Table 4-3. The patient described does not meet the arthritis criteria; thus her only criteria are oral ulcers and weakly positive ANA.

6. The answer is A.

(Chap. 4) The patient has Libman-Sacks endocarditis associated with her SLE. This results in fibrinous endocarditis and can lead to valvular insufficiencies, most often mitral or aortic, or embolism. It is not generally found with concomitant pericarditis, though this is another common cardiac manifestation of systemic lupus erythematosus. Although glucocorticoids and anti-inflammatory therapies have no proven benefit in this condition, they are often used in conjunction with supportive care. Because Libman-Sacks endocarditis is a culture-negative endocarditis and is not thought to be due to microbial infection, blood cultures will not be positive.

7. The answer is D.

(Chap. 4) Systemic lupus erythematosus is a multisystem disease with diverse organ involvement and multiple different manifestations within an organ system. The system most commonly involved is the musculoskeletal system, with 95% of patients having involvement, usually as arthralgias or myalgias. Arthritis is also common and is one of the diagnostic criteria for SLE. Cutaneous and hematologic disease occurs in approximately 80–85% of patients. Neurologic and cardiopulmonary diseases affect approximately 60% of patients, while renal and gastrointestinal diseases occur in less than 50% of cases.

8. The answer is E.

(Chap. 4) Although most clinicians believe that females with SLE should not become pregnant if they have active disease or advanced renal or cardiac disease, the presence of SLE itself is not an absolute contraindication to pregnancy. The outcome of pregnancy is best for females who are in remission at the time of conception. Even in females with quiescent disease, exacerbations may occur (usually in the first trimester and the immediate postpartum period), and 25–40% of these pregnancies end in spontaneous abortion. Fetal loss rates are higher in patients with lupus anticoagulant or anticardiolipin antibodies. Flare-ups should be anticipated and vigorously treated with steroids. Steroids given throughout pregnancy usually have no adverse effects on the child. In this case, the fact that the female had a life-threatening bout of disease a year ago would argue against stopping her drugs at this time. Neonatal lupus, which is manifested by thrombocytopenia, rash, and heart block, is rare but can occur when mothers have anti-Ro antibodies.

9. The answer is C.

(Chap. 4) This patient is presenting with acute lupus nephritis with evidence of hematuria, proteinuria, and an acute rise in creatinine. Together with infection, nephritis is the most common cause of mortality in the first decade after diagnosis of SLE and warrants prompt immunosuppressive therapy. It is important to assess for other potentially reversible causes of acute renal insufficiency, but this patient is not otherwise acutely ill and is taking no medications that would cause renal failure. The urinalysis shows evidence of active nephritis with hematuria and proteinuria. Even in the absence of RBC casts, therapy should not be withheld to await biopsy results in someone with a known diagnosis of SLE with consistent clinical presentation and urinary findings. This patient also has other risk factors known to predict the development of lupus nephritis, including high titers of anti-dsDNA and African-American race. The mainstay of treatment for any life-threatening or organ-threatening manifestation of SLE is high-dose systemic glucocorticoids. Addition of cytotoxic or other immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil) is recommended to treat serious complications of SLE, but their effects are delayed for 3–6 weeks after initiation of therapy, whereas the effects of glucocorticoids begin within 24 hours. Thus, these agents alone should not be used to treat acute, serious manifestations of SLE. The choice of cytotoxic agent is at the discretion of the treating physician. Cyclophosphamide in combination with steroid therapy has been demonstrated to prevent the development of end-stage renal disease better than steroids alone. Likewise, mycophenolate also prevents the development of end-stage renal disease in combination with glucocorticoids, and some studies suggest that African Americans have a greater response to mycophenolate than to cyclophosphamide. Plasmapheresis is not indicated in the treatment of lupus nephritis but is useful in cases of severe hemolytic anemia or thrombotic thrombocytopenic purpura associated with SLE. This patient has no acute indication for hemodialysis and, with treatment, may recover renal function.

10. The answer is E.

(Chap. 4) This patient clearly has a flare of her SLE induced by ultraviolet sunlight, a common inciting factor for lupus flares. It is thought that the UV sunlight induces skin apoptosis that initiates the SLE flare. Furthermore, this patient has severe acute lupus nephritis. Aggressive therapy with high-dose methylprednisolone is life saving and gives the best chance of renal recovery. Therapy for severe lupus derives from studies of lupus nephritis. These have shown that after a "pulse" of high-dose intravenous methylprednisolone, subsequent therapy with prednisone improves renal recovery. Studies of cytotoxic agents in lupus nephritis have been conducted in combination with corticosteroid treatment. These studies have shown that cyclophosphamide, mycophenolate mofetil, and azathioprine have efficiency for induction of improvement in severely ill patients. It appears that African Americans are more likely to respond to mycophenolate. Good improvement of lupus nephritis occurs in 80% of patients receiving cyclophosphamide or mycophenolate at 1–2 years; however, many patients have flares and are more likely to progress to end-stage renal disease. The utility of biologics, including rituximab, in SLE is under vigorous investigation. Some have advocated their use in patients with refractory disease based on open-label studies. Based on this patient's first episode of lupus nephritis, there would not be an indication for rituximab at this point.

11. The answer is A.

(Chap. 5) The patient has multiple clinical manifestations of arterial thrombosis in her hand and brain. Combined with the likely history of placental insufficiency in the three prior pregnancies, the possibility of antiphospholipid antibody syndrome is likely. In addition, she has evidence of acute kidney injury, suggesting multisystem disease. Thrombocytopenia may be due to hemolytic anemia, but the absence of schistocytes makes it less likely that she has thrombotic thrombocytopenic purpura. Although MRI of her brain and extremity duplex may confirm the presence of thrombosis, these will not diagnose antiphospholipid antibody syndrome. An anticardiolipin antibody screening panel will look for evidence of antibodies directed against cardiolipin and β_2 glycoprotein I. Additional testing for lupus anticoagulant determined by clotting assays such as the Russell viper venom time, false-positive RPR, and the aPTT may also be useful. Antinuclear antibody is likely to be positive given the common overlap with systemic lupus erythematosus, but is nonspecific.

12. The answer is D.

(Chap. 5) This patient has a typical presentation of antiphospholipid syndrome (APS) with a deep venous thrombosis (DVT), history of spontaneous abortion, and isolated elevated aPTT due to a lupus anticoagulant. Additional clinical features of APS involving the arterial or venous circulation include livedo reticularis (24%), pulmonary embolism (14%), stroke (20%), transient ischemic attack (TIA) (10%), myocardial infarction (10%), migraine (20%), preeclampsia

(10%), thrombocytopenia (30%), and autoimmune hemolytic anemia (10%). Laboratory criteria include demonstration of lupus anticoagulant (elevated aPTT that does not correct on mixing) in conjunction with the presence of anticardiolipin and/or anti–β_2 glycoprotein I on two occasions 3 months apart. After diagnosis of a thrombotic event due to APS, patients should receive warfarin for life with a goal INR of 2.5–3.5 alone or in combination with daily aspirin. During pregnancy patients should receive heparin plus aspirin. Patients who develop recurrent thrombosis while on effective anticoagulation may benefit from a 5-day infusion of intravenous gamma globulin or 4 weeks of rituximab therapy. The optimal therapy for patients with APS without a thrombotic event is not known; however, daily aspirin (80 mg) protects patients with SLE and antiphospholipid antibodies from thrombotic events. Warfarin for 3 months with an INR goal of 2.0–3.0 is recommended therapy for DVT with a known reversible precipitating event. Warfarin for 6–12 months with an INR goal of 2.0–3.0 is recommended therapy for first-episode idiopathic DVT.

13. The answer is E.

(Chap. 6) Once the disease process of rheumatoid arthritis is established, the most common joints of involvement are the wrists, metacarpophalangeal joints, and proximal interphalangeal joints. Distal interphalangeal joint involvement is rarely due to rheumatoid arthritis and more often due to coexisting osteoarthritis.

14. The answer is C.

(Chap. 6) There is potential involvement of multiple organ systems in RA. The most common pulmonary complication is pleural effusion that is typically exudative and presents with chest pain and dyspnea. RA is associated with a form of diffuse interstitial lung disease that may present with dyspnea and bilateral interstitial infiltrates that may be extensive enough to develop into a honeycomb pattern. Pulmonary nodules associated with RA may be solitary or multiple. They often occur in conjunction with cutaneous nodules. Bronchiectasis and respiratory bronchiolitis may also be due to RA. Many of these manifestations respond to immunosuppressive therapy. Lobar infiltrate has not been described due to RA and is more commonly due to an acute infectious etiology, often as a complication of RA immunosuppressive therapy.

15. The answer is A.

(Chap. 6) Joint imaging is a critical tool for both the diagnosis and monitoring of disease status in RA. Plain radiographs, because of their ready availability and ease of film comparison, are most commonly ordered. The earliest clinical sign of RA is juxta-articular osteopenia, though this may be difficult to appreciate on newer, digitized films. Other findings include soft-tissue swelling, symmetric joint space loss, and subchondral erosions most frequently in the wrists, metacarpophalangeal, and proximal interphalangeal joints, and the metatarsophalangeal joint.

16. The answer is C.

(Chap. 6) The prevalence of RA is 0.8%, and females are three times more likely to be affected than males. However, as the population ages, the prevalence increases and the sex difference diminishes. RA is found throughout the world and affects people of all races. Age of onset is most commonly 35–50 years. Family studies show a clear genetic predisposition. First-degree relatives have approximately four times the expected rate of RA. Other risk factors for RA include the class II major histocompatibility antigen HLA-DR4. Approximately 70% of patients with RA have HLA-DR4. However, this association is not true in Africans or African Americans, among whom 75% do not show this allele. The role of this allele in the pathogenesis of RA remains unknown because the cause of RA is unknown. The earliest lesion in RA is microvascular injury with an increase in the number of synovial lining cells. Increased numbers of mononuclear cells are seen in the synovial lining, and this is thought to be under the control of CD4+T lymphocytes. As the inflammation continues, the articular matrix is degraded by collagenases and cathepsins produced by the inflammatory cells. Other cytokines produced by the inflammatory cells include IL-1 and TNF-α. Over time, bone and cartilage are destroyed, leading to the end-stage clinical manifestations. Rheumatoid factor (RF) is an IgM molecule directed against the Fc portion of IgG and is found in two-thirds of patients with RA. However, this molecule is found in approximately 5% of healthy persons and more than 10% of persons older than age 60. It is not known to have a role in the pathogenesis of the disease, but titers of RF are shown to be predictive of the severity of clinical manifestations or the presence of extraarticular manifestations.

17. The answer is C.

(Chap. 6) Rheumatoid arthritis is chronic, symmetric, inflammatory polyarthritis. In two-thirds of patients, an initial clinical presentation of fatigue, anorexia, and weakness precedes joint complaints. In established RA (i.e., in patients known to be diagnosed

with this disorder), the most common manifestation is pain in affected joints that is worsened by movement. Morning stiffness of an hour or more is very common in these patients as well, but it is worth noting that this clinical finding does not allow differentiation between inflammatory and noninflammatory arthritides. Arthritic pain comes from the joint capsule itself, which is innervated and very sensitive to distention. Ten percent of patients with RA will have a first-degree relative with the disease. Weight loss is a nonspecific symptom and is not definitively associated with active disease.

18. The answer is E.

(Chap. 6) Anemia is common in RA and parallels the degree of inflammation as measured by C-reactive protein or ESR. Felty's syndrome, typically occurring in late-stage, poorly controlled disease, is characterized by the triad of neutropenia, splenomegaly, and rheumatoid nodules. Rheumatoid vasculitis is not common and typically occurs in long-standing disease. It is associated with hypocomplementemia. The cutaneous signs are typical of vasculitic lesions with palpable purpura, digital infarcts, livedo reticularis, and ulcers. Clinical manifestations of pericarditis occur in 10% of patients, with echocardiographic or autopsy findings in about half of those cases. Secondary Sjögren's syndrome manifest as keratoconjunctivitis sicca or xerostomia occurs in approximately 10% of patients with RA. RA also appears to increase the risk of developing B-cell lymphoma by two to four times in the general population. The risk of lymphoma appears to correlate with high levels of disease activity or the presence of Felty's syndrome. Platelet counts in RA are typically elevated in association with the acute phase response of inflammation. Immune thrombocytopenia is rare.

19. The answer is D.

(Chap. 6) The therapy of RA has changed dramatically in the past two decades with the development of drugs that modify the disease course of RA. Methotrexate is the DMARD of first choice for treatment of early RA. Other conventional DMARDs include hydroxychloroquine, sulfasalazine, and leflunomide. Leflunomide, an inhibitor of pyrimidine synthesis, is efficacious as a single agent or in combination with methotrexate. Hydroxychloroquine and sulfasalazine are typically reserved for mild disease. The biologic DMARDs have dramatically improved the treatment of RA in the past decade. There are currently five anti-TNF agents, including infliximab, approved for use in patients with RA. Rituximab, an anti-CD20 antibody, is approved for refractory RA in combination with methotrexate. It is more efficacious in seropositive than seronegative patients. Other biologics approved for use in RA include anakinra (IL-1 receptor antagonist), abatacept (CD28/CD80/86 antagonist), and tocilizumab (IL-6 antagonist). Nonsteroidal anti-inflammatory drugs, including Naprosyn (naproxen), were formally utilized as core RA therapy; however, they are now utilized as adjunctive treatment for symptom management.

20. The answer is D.

(Chap. 7) Acute rheumatic fever (ARF) is almost universally due to group A streptococcal disease at the present time, though virtually all streptococcal disease may be capable of precipitating rheumatic fever. Although skin infections may be associated with rheumatic fever, far and away the most common presentation is with preceding pharyngitis. There is a latent period of approximately 3 weeks from an episode of sore throat to presentation of ARF. The most common manifestations are fever and polyarthritis, with polyarthritis being present in 60–75% of cases. Carditis may also be present, though somewhat less frequently in 50–60% of cases. Chorea and indolent carditis may have a subacute presentation. Chorea is present in 2–30% of affected individuals, while erythema marginatum and subcutaneous nodules are rare. Sixty percent of patients with ARF progress to rheumatic heart disease, with the endocardium, pericardium, and myocardium all potentially involved. All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection.

21. The answer is D.

(Chap. 7) This patient has a history very suggestive of recurrent bouts of ARF with evidence of mitral regurgitation, mitral stenosis, and aortic regurgitation on physical examination. This and the presence of atrial fibrillation imply severe rheumatic heart disease. Risk factors for this condition include poverty and crowded living conditions. As a result, ARF is considerably more common in the developing world. Daily aspirin is the treatment of choice for the migratory large-joint arthritis and fever that are common manifestations of ARF. Practitioners sometimes use steroids during acute bouts of carditis to quell inflammation, though this remains a controversial practice and has no role between flares of ARF. Secondary prophylaxis with either daily oral penicillin or, preferably, monthly IM injections is considered the best method to prevent further episodes of ARF, and therefore prevent further valvular damage.

Primary prophylaxis with penicillin on an as-needed basis is equally effective for preventing further bouts of carditis. However, most episodes of sore throat are too minor for patients to present to a physician. Therefore, secondary prophylaxis is considered preferable in patients who already have severe valvular disease. Doxycycline is not a first-line agent for group A *Streptococcus*, the pathogen that incites ARF.

22. The answer is A.

(Chap. 8) The prognosis for patients with scleroderma renal disease is poor. In SRC patients prompt treatment with an ACE inhibitor may reverse acute renal failure. In recent studies the initiation of ACE inhibitor therapy resulted in 61% of patients having some degree of renal recovery and not needing chronic dialysis support. The survival rate is estimated to be 80–85% at 8 years. Among patients who needed dialysis, when treated with ACE inhibitors, over 50% were able to discontinue dialysis after 3–18 months. Therefore, ACE inhibitors should be used even if the patient requires dialysis support.

23. The answer is D.

(Chap. 9) The patient presented with classic symptoms for Sjögren's syndrome including dry mouth and eyes. This condition may be primary, as in this case, or secondary in association with another connective tissue disease such as scleroderma or rheumatoid arthritis. Many autoantibodies may be demonstrated in the serum of patients with Sjögren's including antibodies to Ro/SS-A or La/SS-b. Sialometry will demonstrate decreased production of saliva, and MRI or MR sialography of the major salivary glands is used also. Ocular involvement with decreased tear production is demonstrated by the Schirmer's I test. Scl-70 antibody is associated with scleroderma and should not be positive in primary Sjögren's syndrome.

24. The answer is A.

(Chap. 9) Although Sjögren's syndrome most commonly affects the eyes and mouth, there are a number of common extraglandular sites of involvement. The most common is arthritis or arthralgias that complicated up to 60% of cases. Raynaud's phenomenon is the second most common extraglandular site. Lung involvement and vasculitis are found in less than 20% of patients. Lymphoma, though a concerning and highly morbid complication, is relatively rare, affecting only 6% of patients with Sjögren's syndrome.

25. The answer is B.

(Chap. 9) The patient in this vignette is presenting with severely dry eyes and mouth in the presence of autoantibodies to Ro and La (SS-A and SS-B, extractable nuclear and cytoplasmic antigens) consistent with the diagnosis of Sjögren's syndrome. This autoimmune disorder is associated with the lymphocytic infiltration of exocrine glands that results in decreased tear and saliva production as the most prominent symptoms. Sjögren's syndrome affects women nine times more frequently than men and usually presents in middle age. Other autoimmune diseases often have associated xerostomia and dry eyes (secondary Sjögren's syndrome). High titers of antibodies to Ro and La are associated with longer disease duration, salivary gland enlargement, and the development of extraglandular involvement, especially cutaneous vasculitis and demyelinating syndromes. One-third of patients with Sjögren's syndrome have extraglandular involvement of the disease, most commonly in the lungs and kidneys. In this patient with acidemia and hypokalemia, the possibility of renal disease due to Sjögren's syndrome should be considered. Interstitial nephritis is a common manifestation of Sjögren's syndrome in the kidneys. Distal (type I) renal tubular acidosis is also frequent, occurring in 25% of individuals with Sjögren's syndrome. Diagnosis could be confirmed by obtaining urine electrolytes to demonstrate a positive urine anion gap. Renal biopsy is not necessary. Treatment does not require immunosuppression as the acidemia can be treated with bicarbonate replacement. Diarrhea could cause similar electrolyte abnormalities with a non–anion gap acidosis, but the patient would be symptomatic. Furthermore, gastrointestinal symptoms do not commonly occur in Sjögren's syndrome. Hypoaldosteronism is associated with a type IV renal tubular acidosis that results in hyperkalemia and a non–anion gap acidosis. Renal compensation for respiratory alkalosis should not result in hypokalemia. Purging in anorexia nervosa could result in hypokalemia and increased risk of dental caries, but it would be associated with metabolic alkalosis rather than acidosis.

26. The answer is D.

(Chap. 9) Lymphoma is well known to develop specifically in the late stage of Sjögren's syndrome. Common manifestations of this malignant condition include persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, and low C4 complement levels. Most of the lymphomas are extranodal, marginal zone B cell, and low grade. Low-grade lymphomas may be detected incidentally during a labial biopsy. Mortality is higher in patients with concurrent B symptoms (fevers, night sweats, and weight loss), a lymph node mass greater than 7 cm, and a high or intermediate histologic grade.

27. The answer is D.
(Chap. 10) Ankylosing spondylitis is closely correlated with the presence of the histocompatibility antigen HLA-B27. In North American whites, the prevalence of B27 is 7%, but in patients with ankylosing spondylitis it is 90%. Not all persons with B27 develop ankylosing spondylitis; the disease is only present in 1–6% of B27-positive individuals.

28. The answer is A.
(Chap. 10) Although the most serious spine complication of ankylosing spondylitis is fracture, there are a number of important extraarticular manifestations. Anterior uveitis is the most common, occurring in 40% of patients with ankylosing spondylitis. Inflammatory bowel disease has been reported to be frequently present. Less common complications include aortic insufficiency, third-degree heart block, pulmonary nodules and upper lobe fibrosis, cardiac dysfunction, retroperitoneal fibrosis, prostatitis, and amyloidosis.

29. The answer is B.
(Chap. 10) Nonsteroidal anti-inflammatory drugs are the first line of pharmacologic therapy for ankylosing spondylitis, of which this patient has a classic presentation. These agents have been shown to reduce pain and tenderness and increase mobility. There is even some evidence that they slow disease progression. Given their proven efficacy, tolerability, and safety, they remain first-line therapy. Anti–TNF-α agents have been reported to have dramatic effects in ankylosing spondylitis, with infliximab, etanercept, adalimumab, and golimumab having published reports of success. Because of their potential side effects, including serious infections, hypersensitivity reactions, and others, these agents should be reserved for patients who fail therapy with NSAIDs.

30. The answer is E.
(Chap. 10) Reactive arthritis refers to an acute, nonpurulent arthritis that occurs after an infection elsewhere in the body. Often presenting with lower joint inflammatory arthritis occurring 1–4 weeks after a diarrheal episode, reactive arthritis may also include uveitis or conjunctivitis, dactylitis, urogenital lesions, and characteristic mucocutaneous lesions such as keratoderma blennorrhagica. The most common organism associated with reactive arthritis is *Shigella* species, although *Yersinia*, *Chlamydia*, and, to a much lesser extent, *Salmonella* and *Campylobacter* have been described.

31. The answer is D.
(Chap. 10) The patient has a spondyloarthritic syndrome with enthesitis and sacroiliitis associated with inflammatory bowel disease. This is a common association called enteropathic arthritis. Generally, enteropathic arthritis responds well to suppression of gastrointestinal disease using anti–TNF-α agents such as infliximab. Other treatments for inflammatory bowel disease are also effective in the resolution of arthritis, such as glucocorticoids and sulfasalazine. NSAIDs may be helpful, but there is significant concern for the precipitation of flares of inflammatory bowel disease and precipitation of ulcers.

32. The answer is E.
(Chap. 10) Whipple's disease is a rare chronic bacterial infection of the gastrointestinal tract most commonly affecting middle-aged men. Arthritis is a common early manifestation of the disease, with arthritis predating gastrointestinal symptoms by 5 years or more. Large and small joints may be affected and sacroiliitis is common. Arthritis is often migratory and lasts several days with spontaneous recovery. Synovial fluid is generally inflammatory. Radiographs rarely show joint erosions, though sacroiliitis may be demonstrated. Diagnosis is often made by PCR amplification of genetic material from *Tropheryma whippelii* in biopsied material, most commonly the gut.

33. The answer is D.
(Chap. 10) Although anti–TNF-α drugs such as infliximab are potent and relatively safe, several types of side effects are not rare. These include serious infections such as disseminated tuberculosis, fungal (histoplasmosis, aspergillus, pneumocystis) and bacterial (legionella, pneumococcus) infections, hematologic disorders such as pancytopenia, demyelinating disorders, systemic lupus erythematosus-related autoantibodies, and potential risk of lymphoma. Additionally, clinical features such as exacerbation of congestive heart failure, hypersensitivity infusion or injection site reactions, and severe liver disease have been described. There are some isolated reports of hypersensitivity pneumonitis, but these are confounded by coadministration of known pulmonary toxic agents.

34. The answer is B.
(Chap. 10) Enthesopathy or enthesitis is the term used to describe inflammation at the site of tendinous or ligamentous insertion into bone. This type of inflammation is seen most frequently in patients with seronegative spondyloarthropathies and various infections, especially viral infections. The other definitions apply to other terms used in the orthopedic and rheumatic examination. Subluxation is the alteration of joint alignment so that articulating surfaces incompletely approximate each other. Synovitis refers

to the inflammation of the periarticular membrane lining the joint capsule. Inflammation of a saclike cavity near a joint that decreases friction is the definition of bursitis. Finally, crepitus is a palpable vibratory or crackling sensation elicited with joint motion.

35. The answer is C.

(Chap. 10) This patient complains of symptoms consistent with a diagnosis of fibromyalgia. Patients with fibromyalgia frequently complain of diffuse body pain, stiffness, paresthesias, disturbed sleep, easy fatigability, and headache. The prevalence of fibromyalgia is approximately 3.4% of females and 0.5% of males. This disorder is thought to represent a disturbance of pain perception. Disturbed sleep with a loss of stage 4 sleep has been implicated as a factor in the pathogenesis of the disease. Serotonin levels in the cerebrospinal fluid have also commonly been seen and may play a role in the pathogenesis. A diagnosis of fibromyalgia is based on the American College of Rheumatology criteria, which combine symptoms and physical examination. The patient must exhibit diffuse pain in all areas of the body with tenderness to palpation at 11 of 18 designated tender point sites. These sites include the occiput, trapezius, cervical spine, lateral epicondyles, supraspinatus muscle, second rib, gluteus, greater trochanter, and knee. Digital palpation should be performed with a moderate degree of pressure. Examination of the joints shows no evidence of inflammatory arthropathy. There are no laboratory tests that are specific for the diagnosis. Positive antinuclear antibodies may be seen, but at the same frequency as in the normal population. HLA-B27 is found in 7% of the white population, but only 1–6% of people with HLA-B27 will develop ankylosing spondylitis. Radiograms are normal in these patients.

36. The answer is D.

(Chap. 10) This patient shows the typical features of psoriatic arthritis. Five to ten percent of patients with psoriasis will develop an arthritis associated with the rash. In 60–70% of cases, the rash precedes the diagnosis. However, another 15–20% of patients will have joint complaints as the presenting symptom of their psoriasis. The disease typically begins in the fourth or fifth decade of life. Psoriatic arthritis has varied joint presentations with five commonly described patterns of joint involvement: (1) arthritis of the distal interphalangeal (DIP) joints, (2) asymmetric oligoarthritis, (3) symmetric polyarthritis similar to RA, (4) axial involvement, and (5) arthritis mutilans with the typical "pencil in cup" deformity seen on hand radiography. Erosive joint disease ultimately develops in almost all these patients, and most of them become disabled. Nail changes are prominent in 90% of patients with psoriatic arthritis. Changes that are frequently seen include pitting, horizontal ridging, onycholysis, yellowish discoloration of the nail margins, and dystrophic hyperkeratosis. The diagnosis of psoriatic arthritis is primarily clinical. Thus, in patients with joint symptoms that precede the onset of rash, the diagnosis is frequently missed until dermatologic or nail changes develop. A family history of psoriasis is important to ascertain in any patient with an undiagnosed inflammatory polyarthropathy. The differential diagnosis of DIP arthritis is short; only osteoarthritis and gout are commonly seen in these joints. Radiography may show typical changes, particularly in patients with arthritis mutilans. Treatment is directed at both the rash and the joint disease simultaneously. Anti–TNF-α therapy has recently been shown to be helpful for both the dermatologic and joint manifestations of disease. Other treatments include methotrexate, sulfasalazine, cyclosporine, retinoic acid derivatives, and psoralen plus ultraviolet light.

37. The answer is E.

(Chap. 11) Although the molecular pathology of most vasculitic syndromes is poorly understood, the deposition of immune complexes is commonly thought to play an important role in vasculitis associated with IgA vasculitis (Henoch-Schönlein) cryoglobulinemic vasculitis associated with hepatitis C, serum sickness and cutaneous vasculitic syndromes, and polyarteritis nodosa–like vasculitis associated with hepatitis B. Granulomatosis with polyangiitis (Wegener's), Eosinophilic granulomatosis with polyangiitis (Churg-Strauss), and microscopic polyangiitis are thought to be due to production of antineutrophilic antibodies. Pathogenic T lymphocyte responses are also implicated in giant cell arteritis, Takayasu's arteritis, granulomatosis with polyangiitis (Wegener's), and Eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

38. The answer is E.

(Chap. 11) ANCAs are antibodies directed at proteins in the cytoplasmic granules of neutrophils and monocytes. cANCA, or cytoplasmic ANCA, is directed against proteinase-3, a proteinase present in neutrophil azurophilic granules. More than 90% of patients with granulomatosis with polyangiitis (Wegener's) will be cANCA positive. cANCA can also be seen in microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Perinuclear ANCA or pANCA refers to a more localized perinuclear staining pattern and antibodies are most commonly directed against myeloperoxidase, though other antigens have been described. pANCA has been reported in variable percentages in microscopic

polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), and granulomatosis with polyangiitis (Wegener's) and its variants. Additionally, pANCA staining that is not due to antimyeloperoxidase antibodies has been described in a number of other conditions including rheumatic and nonrheumatic autoimmune disease and inflammatory bowel disease. In this patient with a positive cANCA who has a nasal septal perforation, glomerulonephritis, and a normal eosinophil count, this is clinically more consistent with granulomatosis with polyangiitis (Wegener's) than microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

39. The answer is D.

(Chap. 11) The patient presents with classic symptoms for granulomatosis with polyangiitis (Wegener's), also known as granulomatosis with polyangiitis. The average age of diagnosis is 40 years and there is a male predominance. Upper respiratory symptoms often predate lung or renal findings and may even present with septal perforation. The diagnosis is made by demonstration of necrotizing granulomatous vasculitis on biopsy. Pulmonary tissue offers the highest yield. Biopsy of the upper airway usually shows the granulomatous inflammation but infrequently shows vasculitis. Renal biopsy may show the presence of pauci-immune glomerulonephritis.

40. The answer is C.

(Chap. 11) The patient has a classic presentation for giant cell arteritis with associated polymyalgia rheumatica including headache, jaw claudication, and visual disturbances. Her age makes this diagnosis highly likely as well. The diagnosis is confirmed by temporal artery biopsy; however, in the presence of visual symptoms, initiation of therapy should not be delayed pending a biopsy, as the biopsy may be positive even after approximately 14 days of glucocorticoid therapy. Delay in therapy risks irreversible visual loss. Additionally, a dramatic response to therapy may lend further support to the diagnosis. The primary therapy is prednisone at 40–60 mg daily for 1 month with gradual tapering. Although erythrocyte sedimentation rate is nearly universally elevated, it is not specific for the diagnosis. Temporal artery ultrasound may be suggestive but is not diagnostic.

41. The answer is C.

(Chap. 11) The most common manifestations of cryoglobulinemic vasculitis are cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis. The demonstration of circulating cryoprecipitates is a critical component of the diagnosis, and often rheumatoid factor can be found as well. Because hepatitis C infection is present in the vast majority of patients with cryoglobulinemic vasculitis, infection should be sought in all patients with this clinical syndrome.

42. The answer is E.

(Chap. 11) This patient has polyarteritis nodosa associated with hepatitis B infection. Polyarteritis nodosa (PAN) is a small- and medium-vessel vasculitis that classically involves the muscular mesenteric and renal arteries. Pulmonary arteries are spared. Classic PAN is a rare disease, but its exact prevalence is unknown because reported cases frequently also include other vasculitides such as microscopic polyangiitis. Prior to the Chapel Hill Consensus Conference of 1992, microscopic polyangiitis and PAN were considered as the same disease, but it has been recognized that these are two separate diseases with different serologic markers and vascular predilection. Clinical manifestations of PAN are commonly vague, and often patients have been ill for several months prior to diagnosis. Symptoms include fatigue, weight loss, abdominal pain, headache, and hypertension. The pathologic lesion of PAN is necrotizing inflammation of the small- and medium-sized muscular arteries, and diagnosis relies on demonstration of this lesion on biopsy. However, in the absence of easily obtainable tissue, the presence of multiple aneurysmal dilatations on mesenteric angiogram is highly suggestive of PAN in the appropriate clinical setting. There are no serologic tests that are diagnostic of PAN. It is rare to have positive antibodies to pANCA or cANCA in PAN. Interestingly, 30% of cases of PAN are associated with active hepatitis B infection, as in this patient, and it is thought that circulating immune complexes may play a role in the pathogenesis of this disease. Unlike PAN, microscopic polyangiitis (MPA) involves venules and capillaries in addition to small arteries. The histopathologic lesion of MPA is a necrotizing vasculitis that is pauci immune with minimal deposition of immune complexes. Typical presenting features are rapidly progressive glomerulonephritis and pulmonary hemorrhage, which are distinctly uncommon features of PAN. Antimyeloperoxidase antibodies (pANCA) are frequently present. Mixed cryoglobulinemia is a small-vessel vasculitis most often associated with hepatitis C infection. Skin involvement with leukocytoclastic vasculitis and palpable purpura are the most common presenting features. Proliferative glomerulonephritis is present in 20–60% of individuals and is the most common cause of morbidity. Ischemic colitis typically presents with abdominal pain out of proportion to the examination as in this case, but the

mesenteric angiogram would show atherosclerotic narrowing rather than aneurysmal dilatation. Hepatocellular carcinoma is not associated with vasculitis and typically presents with vague abdominal pain and obstructive jaundice.

43. The answer is C.

(Chap. 11; JW Newberger et al: Circulation 110:2747, 2004.) The most likely cause of the acute coronary syndrome in this patient is thrombosis of a coronary artery aneurysm in an individual with a past history of Kawasaki disease. Kawasaki disease is an acute multisystem disease that primarily presents in children less than 5 years of age. The clinical manifestations in childhood are nonsuppurative cervical lymphadenitis; desquamation of the fingertips; and erythema of the oral cavity, lips, and palms. Approximately 25% of cases are associated with coronary artery aneurysms that occur late in illness in the convalescent stage. Early treatment (within 7–10 days of onset) with IV immunoglobulin and high-dose aspirin decreases the risk of developing coronary aneurysms to about 5%. Even if coronary artery aneurysms develop, most regress over the course of the first year if the size is smaller than 6 mm. Aneurysms larger than 8 mm, however, are unlikely to regress. Complications of persistent coronary artery aneurysms include rupture, thrombosis and recanalization, and stenosis at the outflow area. Dissection of the aortic root and coronary ostia is a common cause of death in Marfan's syndrome and can also be seen with aortitis due to Takayasu's arteritis. In this patient, there is no history of hypertension, limb ischemia, or systemic symptoms that would suggest an active vasculitis. In addition, there are no other ischemic symptoms that would be expected in Takayasu's arteritis. Myocardial bridging overlying a coronary artery is seen frequently at autopsy but is an unusual cause of ischemia. The possibility of cocaine use as a cause of myocardial ischemia in a young individual must be considered, but given the clinical history it is a less likely cause of ischemia in this case.

44. The answer is C.

(Chap. 12) Recurrent oral ulceration is required for the diagnosis of Behçet's disease. The ulcers may be single or multiple, are shallowly based with a yellow necrotic base, and are painful. They are generally small, less than 10 mm in diameter. The diagnosis of Behçet's also requires two of the following: recurrent genital ulceration, eye lesions, skin lesions, and pathergy test. Nonspecific skin inflammatory reactivity to any scratches or intradermal saline injection (pathergy test) is common and specific.

45 and 46. The answers are A and C, respectively.

(Chap. 12) Behçet's syndrome is a multisystem disorder of uncertain cause that is marked by oral and genital ulcerations and ocular involvement. This disorder affects males and females equally and is more common in persons of Mediterranean, Middle Eastern, and Far Eastern descent. Approximately 50% of these persons have circulating autoantibodies to human oral mucosa. The clinical features are quite varied. The presence of recurrent aphthous ulcerations is essential for the diagnosis. Most of these patients have primarily oral ulcerations, although genital ulcerations are more specific for the diagnosis. The ulcers are generally painful, can be shallow or deep, and last for 1–2 weeks. Other skin involvement may occur, including folliculitis, erythema nodosum, and vasculitis. Eye involvement is the most dreaded complication because it may progress rapidly to blindness. It often presents as panuveitis, iritis, retinal vessel occlusion, or optic neuritis. This patient also presents with superficial venous thrombosis. Superficial and deep venous thromboses are present in one-fourth of these patients. Neurologic involvement occurs in up to 10%. Laboratory findings are nonspecific with elevations in the erythrocyte sedimentation rate and the white blood cell count. Treatment varies with the extent of the disease. Patients with mucous membrane involvement alone may respond to topical steroids. In more serious or refractory cases, thalidomide is effective. Other options for mucocutaneous disease include colchicines and intralesional interferon α. Ophthalmologic or neurologic involvement requires systemic glucocorticoids and azathioprine or cyclosporine. Life span is usually normal unless neurologic disease is present. Ophthalmic disease frequently progresses to blindness.

47. The answer is C.

(Chap. 13) Relapsing polychondritis is a disease of unknown cause characterized by inflammation of the cartilage predominantly in the ears, nose, and laryngotracheobronchial tree. Although it may be a primary disorder, relapsing polychondritis is often associated with a number of other conditions including systemic vasculitis, systemic lupus erythematosus, Sjögren's syndrome, spondyloarthritides, Behçet's disease, inflammatory bowel disease, primary biliary cirrhosis, and myelodysplastic syndrome. It is not associated with scleroderma, which causes distinct skin changes that are typically not inflammatory and are not associated with cartilaginous inflammatory disease.

48. The answer is E.

(Chap. 13) Relapsing polychondritis most often presents with recurrent painful swelling of the ear.

Although other cartilaginous sites may be involved such as the nose and the tracheobronchial tree, these are less frequent. Episodes of ear involvement may result in floppy ears. Typically, the pinna is affected while the earlobe is spared, as there is no cartilage in the lobe. Cogan's syndrome is a rare vasculitic syndrome involving hearing loss, but cartilage inflammation is not a feature. Recurrent trauma or irritation is a consideration but the history is not suggestive, and would be less likely to be bilateral and accompanied by inflammatory findings and a relatively spared ear lobe.

49. The answer is A.

(Chap. 14) The finding of noncaseating granulomas is highly suggestive of sarcoidosis, but not confirmatory. To make a specific diagnosis, two or more organs must be affected; however, a suggestive radiograph and positive biopsy are often adequate. Prior to a definitive diagnosis, however, other conditions that may cause noncaseating granulomas should be ruled out. These include beryllium exposure, often in workers in the nuclear industry; atypical mycobacterial infection; and fungal infection such as histoplasmosis. Many malignancies, including testes, and a number of lymphomas may have granulomas, particularly in reactive areas near tumor deposits. Adequate tissue sampling must be ensured to rule out malignancy. Pulmonary alveolar proteinosis is a disease characterized by PAS-positive protein deposits in the alveolar spaces. It is not typically associated with acute or chronic inflammation in the absence of secondary infection.

50. The answer is A.

(Chap. 14) Hypercalcemia and/or hypercalciuria occurs in approximately 10% of patients with sarcoidosis and is thought to be due to increased production of 1, 25-dihydroxyvitamin D by the granuloma itself, with resultant increased gut calcium absorption. Sun and exogenous vitamin D can exacerbate the problem. Because of this, renal calculi are relatively common. If a patient with sarcoidosis is to begin therapy with calcium supplementation, 24-hour urine for calcium excretion should be performed before and after initiation of therapy. Often small doses of glucocorticoids are adequate to control this problem.

51. The answer is A.

(Chap. 14) The treatment of sarcoidosis depends on whether it is in the acute or chronic form. In many cases, acute disease without abnormalities of neurologic, cardiac, ocular, or metabolic systems may not require therapy. The mainstay of systemic therapy remains to be glucocorticoids. In the chronic form, treatment is dependent on the response to corticosteroids and the tolerability of tapering to low doses (<10 mg/d). Hydroxychloroquine has been shown to be effective in skin disease due to sarcoidosis. Methotrexate works in approximately two-thirds of patients, regardless of disease manifestations. Azathioprine is another cytotoxic agent that is often used in chronic disease, although the evidence in support of this therapy is mostly retrospective. Prospective studies of etanercept and infliximab in patients have shown that etanercept has a limited role as a steroid-sparing agent. In contrast, infliximab, when added to a regimen including prednisone and a cytotoxic agent, improved lung function. The difference in responses to these anti-TNF agents may have to do with the difference in mechanism (receptor antagonism vs. antibody).

52. The answer is A.

(Chap. 14) Sarcoidosis is often discovered on routine chest radiograph by the presence of bilateral hilar adenopathy, often in asymptomatic patients. The Scadding method of scoring the standard chest radiograph is still utilized despite CT being more sensitive. Stage 1 is hilar adenopathy (+/− right paratracheal adenopathy) alone; stage 2 is adenopathy plus parenchymal infiltrates; stage 3 is parenchymal infiltrates alone; and stage 4 is fibrosis. When parenchymal disease is present, the upper lobes often predominate in contrast to most other lung disorders. Skin involvement includes erythema nodosum, maculopapular lesions, hyper- and hypopigmentation, keloid formation, subcutaneous nodules, and lupus pernio. Erythema nodosum is usually seen in the acute form of sarcoidosis and often portends a positive prognosis. Liver involvement is difficult to assess. Granulomas may be seen in over 50% of liver biopsies in patients with sarcoidosis, but approximately 20% have evidence by laboratory studies. The typical pattern is an elevation of alkaline phosphatase typical of all forms of granulomatous hepatitis. There may be some accompanying elevation of transaminases. Eye disease is most commonly anterior uveitis, although posterior (retinal and pars planitis) involvement may occur. There is a marked racial difference in eye involvement due to sarcoidosis. In Japan, over 70% of patients have eye disease, whereas in the United States the prevalence is about 30% (with it being more common in African Americans than white Americans). Cardiac involvement varies dramatically by race. In the United States and Europe, less than 5% of patients develop cardiac disease, whereas in Japan the prevalence is over 25%. There is no difference between whites and African Americans. Cardiac manifestations are conduction and systolic dysfunction due to granulomatous inflammation and infiltration.

53. The answer is C.

(Chap. 18) Inflammatory arthritis can have a variety of causes, either acute or chronic, and affect single or multiple joints. Acute causes of inflammatory arthritis most commonly include infectious etiologies (*Neisseria gonorrhoeae*, septic arthritis, Lyme disease) and crystal-induced arthropathies (gout, pseudogout). Chronic inflammatory arthritis is more likely to be related to autoimmune diseases such as rheumatoid arthritis, reactive arthritis, or psoriatic arthritis. A frequent feature of inflammatory arthritis is the presence of morning stiffness. The stiffness of inflammatory arthritis is more severe after a prolonged rest period, which is why it is characteristically worse in the morning. The stiffness can persist as long as an hour or more, is quite severe, and improves with movement. In contrast, noninflammatory arthritis such as osteoarthritis is more typically associated with stiffness that occurs after a brief rest, lasts less than 60 minutes, and worsens with increased activity. Individuals with inflammatory arthritis also frequently have associated systemic symptoms such as fatigue, fever, rash, or weight loss. On physical examination, one should observe the affected joints for signs of inflammation including redness, swelling, warmth, and pain with movement. Nonspecific laboratory evidence of inflammation is often present, including elevation of erythrocyte sedimentation rate, C-reactive protein, and platelet count, anemia of chronic disease or hypoalbuminemia.

54. The answer is A.

(Chap. 18) Rotator cuff tendinitis or tear is a common cause of shoulder pain. The rotator cuff is formed by the tendons of four muscles that attach to the humerus. These muscles are responsible for stabilizing the humerus within the glenohumeral joint and are important in lifting and rotating the arm, especially in abduction. The muscles that comprise the rotator cuff are the supraspinatus, infraspinatus, teres minor, and subscapularis muscles. In young individuals, it is uncommon to have a complete tear of the rotator cuff unless there is trauma. In most cases, rotator cuff tendinitis is the more common cause of pain due to rotator cuff injuries. Rotator cuff tendinitis is demonstrated by pain with active, but not passive, abduction of the arm. Other symptoms of rotator cuff tendinitis include pain over the lateral deltoid muscle, night pain, and the impingement sign. The impingement sign is positive if pain is elicited with forward flexion of the arm at less than 180°. However, individuals who engage in activities that cause repetitive stress to the rotator cuff can develop tears in the tendons that would require surgery. Examples of such activities include baseball, rowing, and tennis. To evaluate for a tear of the rotator cuff, the arm is passively abducted and the individual is asked to maintain the arm in abduction. The test is positive if the individual is not able to maintain the arm at 90° of abduction. Pain with palpation over the bicipital groove is a sign of bicipital tendinitis. Pain with palpation anteriorly when the arm is rotated internally and externally is a sign of problems within the glenohumeral joint.

55. The answer is B.

(Chap. 18) This patient has degenerative arthritis. His obesity predisposes him to degenerative joint disease that will be worse in the large weight-bearing joints. The physical examination findings of decreased range of motion, crepitus, and varus deformity that is exacerbated on weight bearing are consistent with this diagnosis. The radiogram of the knee demonstrates narrowing of the joint space with osteophyte formation. Occasional effusions may be seen, especially after overuse injuries. The joint fluid analysis in patients with degenerative disease reveals a clear, viscous fluid with a white blood cell count less than 2000/μL. Positively birefringent crystals on polarizing light microscopy will be seen in pseudogout that most commonly affects the knee, whereas negatively birefringent crystals are characteristic of gout. Joint fluid in these inflammatory conditions would generally have a white blood cell count of less than 50,000/μL and is yellow and turbid in character. Septic arthritis presents with fevers and a very warm and tender joint. The joint fluid can have the appearance of frank pus and is opaque. The white blood cell count is usually higher than 50,000/μL and can have a positive Gram stain for organisms.

56. The answer is B.

(Chap. 18) Inflammation of the abductor pollicis longus and the extensor pollicis brevis at the radial styloid process tendon sheath is known as De Quervain's tenosynovitis. Repetitive twisting of the wrist can lead to this condition. Pain occurs when grasping with the thumb and can extend radially along the wrist to the radial styloid process. Mothers often develop this tenosynovitis by holding their babies with the thumb outstretched. The Finkelstein sign is positive in De Quervain's tenosynovitis. It is positive if the patient develops pain by placing the thumb in the palm, closing the fingers around the thumb and deviating the wrist in the ulnar direction. Management of De Quervain's tenosynovitis includes nonsteroidal anti-inflammatory drugs and splinting. Glucocorticoid injections can be effective. A Phalen

maneuver is used to diagnose carpal tunnel syndrome and does not elicit pain. The wrists are flexed for 60 seconds to compress the median nerve to elicit numbness, burning, or tingling. Gouty arthritis will present as an acutely inflamed joint with crystal-laden fluid. Rheumatoid arthritis is a systemic illness with characteristic joint synovitis and radiographic features.

57. The answer is A.

(Chap. 19) Osteoarthritis (OA) is one of the most common causes of disability among older adults and is more common among women than men. OA characteristically affects some joints but spares others. The joints in the hands most commonly affected by OA are the distal and proximal interphalangeal joints and the base of the thumb. It is uncommon for OA to affect the wrist. In addition, OA also is more common in the hips, knees, and cervical and lumbosacral spine. The pain that occurs in OA occurs during or just after joint use, gradually resolving with rest. Thus, the pain of OA in the hands would be expected to be worse while preparing meals (option C) or sewing. The stiffness of OA is not prominent in the mornings as is common in inflammatory arthritis. Rather, stiffness in OA is most marked following brief periods of rest. It can also be associated with the gel phenomenon in which a joint can lock following brief rest periods. On physical examination of the hands of an individual with OA, one may note the presence of bony swellings of the distal and proximal interphalangeal joints. These are known as Heberden's and Bouchard's nodes, respectively. No blood tests are routinely required for the evaluation of OA when the history and physical examination are consistent with the diagnosis. If radiographs are performed, one would expect joint space narrowing due to loss of cartilage. In addition, osteophytes and bony enlargement can be seen. Findings of joint swelling, warmth, and erythema are more common in inflammatory causes of arthritis, and furthermore, it would be unlikely for OA to affect only the wrists.

58. The answer is A.

(Chap. 19) Osteoarthritis (OA) represents joint failure in which pathologic changes have occurred in all structures of the affected joint. The central pathology in OA is articular cartilage loss. The components leading to the development of OA can be separated into those that contribute to joint loading and those that increase joint vulnerability. The most potent risk factor for OA is aging, which affects joint vulnerability. Radiographic evidence of OA is rare in individuals younger than 40; however, more than 50% of individuals older than 70 will have changes of OA. A young joint has in place protective mechanisms that allow it to tolerate excessive loading without lasting damage. Specifically, the cartilage of younger joints is more responsive to dynamic loading, whereas older cartilage fails to respond, leading to breakdown of the cartilage matrix. Women are more susceptible to OA than men, especially after the sixth decade, but the relationship is not as strong as with aging and OA. Joint injury is a strong predictor of the future development of osteoarthritis. Obesity is a well-recognized risk factor in hip and knee arthritis likely due to increased loading forces. Obesity appears to play a role in OA of the hand as well, suggesting that obesity has both a mechanical and metabolic mechanism of action. The genetics of OA are not well understood. Inherited polymorphisms appear to play a role in hand and hip OA, but not as much in other joints.

59. The answer is E.

(Chap. 19) This patient presents with symptoms suggestive of OA. OA is primarily a disease that is mechanically driven, and nonpharmacologic therapy should be a first-line treatment for disease that is mild or intermittent. Avoiding activities that cause pain and overload the joint, strengthening and conditioning the adjacent muscle groups, and supporting or unloading the joint with a brace or crutch are all examples of fundamental treatments aimed at reversing the pathophysiology of OA. In this patient, weight loss should be the primary goal of therapy. Each pound of weight increases loading across a weight-bearing joint three- to six-fold. This patient would benefit from a daily minimal-weight-bearing exercise regimen combined with nutritional goals aimed at slow, consistent weight loss. Avoidance of walking is impractical; a cane or supportive device to lessen the joint load can be offered. Steroids and narcotics are not indicated in this case.

60. The answer is C.

(Chap. 20) This individual has had three recent acute gout attacks and has risk factors for recurrence including chronic kidney disease and the need for diuretic therapy. In this setting, he demonstrates elevation of his uric acid levels. When considering initiation of hypouricemic therapy, one should consider the number of attacks, the serum uric acid levels outside of an acute attack, and the patient's willingness to commit to lifelong therapy. In addition, individuals with uric acid stones or tophaceous gout should also receive hypouricemic therapy. Current agents that are commonly used to treat

hyperuricemia include uricosuric agents and xanthine oxidase inhibitors. Probenecid is the most commonly used uricosuric agent. It is started at a dose of 250 mg twice daily, but can be titrated as high as 3 g daily. However, it is generally not effective when the serum creatinine is greater than 2.0 mg/dL. Benzbromarone is a uricosuric agent that is more effective in individuals with renal failure, but it is not available in the United States. The medication most commonly prescribed in individuals with recurrent gout is allopurinol. This xanthine oxidase inhibitor lowers serum uric acid levels in overproducers, but has multiple associated toxicities including toxic epidermal necrolysis, bone marrow suppression, and renal failure. The initial starting dose is typically 300 mg daily and can be increased to as high as 800 mg daily. However, caution must be taken in individuals with renal failure. Febuxostat is a newer chemically unrelated xanthine oxidase inhibitor. It has been demonstrated to lower uric acid levels as effectively as allopurinol. The initial dose of febuxostat is 40–80 mg daily, and dose adjustment is not required in mild to moderate renal failure. Colchicine is a microtubule stabilizer that decreases inflammation in acute gout attacks. It does not affect levels of uric acid. However, it is commonly used as adjunctive therapy in individuals to prevent gout flares that occur as uric acid levels decline. Indomethacin is a nonsteroidal anti-inflammatory agent that is commonly used in acute gout flares. It does not have a role in the treatment of hyperuricemia or outside of the acute gout attack. Caution should be taken in using nonsteroidal anti-inflammatory drugs in individuals with renal insufficiency.

61. The answer is C.

(Chap. 20) Acute gouty arthritis is frequently seen in individuals on diuretic therapy. Diuretics result in hyperuricemia through enhanced urate reabsorption in the proximal tubule of the kidney in the setting of volume depletion. Hyperuricemia remains asymptomatic in many individuals but may manifest as acute gout. Acute gout is an intensely inflammatory arthritis that frequently begins at night. While any joint may be affected, the initial presentation of gout is often in the great toe at the metatarsophalangeal joint. There is associated joint swelling, effusion, erythema, and exquisite tenderness. A typical patient will complain that the pain is so great that he or she is unable to wear socks or allow sheets or blankets to cover the toes. Arthrocentesis will reveal an inflammatory cloudy-appearing fluid. The diagnosis of gout is confirmed by the demonstration of monosodium urate crystals seen both extracellularly and intracellularly within neutrophils. Monosodium urate crystals appear strongly negatively birefringent under polarized light microscopy and have a typical needle- and rod-shaped appearance. The WBC count is usually below 50,000/μL with values above 100,000/being more likely to be associated with a septic arthritis. Likewise, very low glucose levels and a positive Gram stain are not manifestations of acute gout but are common in septic arthritis. Calcium pyrophosphate dihydrate crystals appear as weakly positively birefringent rhomboidal crystals and are seen in pseudogout.

62. The answer is A.

(Chap. 21) This patient presents with a history consistent with a true septic arthritis due to gonococcal infection. Although gonococcal infection has generally declined in incidence in the past several decades, *Neisseria gonorrhoeae* is responsible for about 70% of acute infectious arthritis in individuals younger than 40 years. Women are two to three times more likely to develop disseminated gonococcal infection than men, likely related to the fact that asymptomatic cervical infection is more common in women. Women appear to be at greatest risk for disseminated gonococcal infection during menses or pregnancy. Disseminated gonococcal infection presents with fevers, chills, migratory arthritis and tenosynovitis, and a papular rash on the trunk and the extensor surfaces of the distal extremities. The rash can progress to hemorrhagic pustules. The joint symptoms and rash are thought to represent immune-complex deposition. In disseminated gonococcal infection, the synovial fluid from inflamed joints usually contains only 10,000–20,000 leukocytes/μL. In this setting, synovial cultures are negative and blood cultures are positive less than 45% of the time.

In this patient, there is evidence of a true septic arthritis with involvement of a single joint and a high leukocyte count (>50,000/μL). Septic arthritis due to *N. gonorrhoeae* is less common than disseminated gonococcal infection but always follows this syndrome. In the clinical scenario presented, the symptoms of fevers, chills, migratory arthralgias, and rash occurred 3 weeks prior to presentation with monoarticular septic arthritis. Blood cultures are almost always negative, and synovial fluid cultures are positive less than 40% of the time. The diagnostic procedure of choice is a culture of a potentially infected mucosal site, including the cervix, urethra, or pharynx.

Individuals with Lyme disease who are untreated frequently develop joint symptoms. Most commonly, this presents as waxing and waning episodes of mono- or oligoarthritis. Ten percent of individuals can

develop an inflammatory erosive arthritis that leads to destructive disease of the joint if untreated. This patient's symptoms are not consistent with Lyme arthritis and testing for *Borrelia burgdorferi* is not indicated. Likewise, this patient presents with findings of monoarticular arthritis, which is not consistent with rheumatoid arthritis, and a rheumatoid factor is not indicated.

63. The answer is B.

(Chap. 21) Although the crystals suggest that the patient may have active pseudogout, the more important acute medical problem is septic arthritis. This is highly probable based on the joint leukocyte count above 100,000/μL, high percentage of PMNs, and positive Gram stain. Crystal-induced, rheumatoid, and other noninfectious causes of arthritis typically have WBC counts in the 30,000–50,000/μL range. WBC counts in indolent infections such as fungal or mycobacterial arthritis are commonly in the 10,000–30,000/range. The bacteria of septic arthritis usually enter the joint via hematogenous spread through synovial capillaries. Patients with rheumatoid arthritis are at high risk of a septic arthritis due to *Staphylococcus aureus* because of chronic inflammation and glucocorticoid therapy. The concurrent presence of pseudogout does not preclude the diagnosis of septic arthritis. In adults, the most common bacterial pathogens are *Neisseria gonorrhoeae* and *S. aureus*. Antibiotics, prompt surgical evaluation for drainage, and blood cultures to rule out bacteremia are all indicated. Prompt local and systemic treatment of infection can prevent the destruction of cartilage, joint instability, or deformity. Direct instillation of antibiotics into the joint fluid is not necessary. If the smear shows no organisms, a third-generation cephalosporin is reasonable empirical therapy. In the presence of gram-positive cocci in clusters, antistaphylococcal therapy should be instituted based on the community prevalence of methicillin resistance or recent hospitalization (which would favor empirical vancomycin). Typically, acute flairs of pseudogout can be addressed with glucocorticoids. However, this could portend a higher risk in the context of infection. Nonsteroidal anti-inflammatory agents might be a possibility depending on the patient's renal function and gastrointestinal history.

64. The answer is C.

(Chap. 22) This patient presents with a characteristic history for fibromyalgia, a diffuse pain syndrome associated with increased sensitivity to evoked pain. The underlying pathophysiology of pain in fibromyalgia is felt to be related to altered pain processing in the central nervous system. Epidemiologically, women are affected nine times more frequently than men. The worldwide prevalence of fibromyalgia is 2–3%, but in primary care practices it is as high as 5–10%. The disorder is even more common in patients with degenerative or inflammatory rheumatic disorders, with a prevalence of 20% or higher. The most common presenting complaint is diffuse pain that is difficult to localize. Pain is both above and below the waist and affects the extremities as well as the axial skeleton. However, it does not localize to a specific joint. The pain is noted to be severe in intensity, difficult to ignore, and interferes with daily functioning. While this patient demonstrates pain at several tender points, the American College of Rheumatology no longer includes tender point assessment in the diagnostic criteria for fibromyalgia. Rather, the new criteria focus on clinical symptoms of widespread pain and neuropsychological symptoms that have been present for at least 3 months. Some of the neuropsychological conditions that are frequently observed in fibromyalgia include sleep disturbance, impaired cognitive functioning, fatigue, stiffness, anxiety, and depression. The lifetime prevalence of mood disorders in patients with fibromyalgia is 80%. Sleep disturbances can include difficulty falling asleep, difficulty staying asleep, and nonrestorative sleep, among others.

65. The answer is D.

(Chap. 22) Fibromyalgia is a common disorder affecting 2–5% of the population. It presents as a diffuse pain syndrome with associated neuropsychological symptoms including depression, anxiety, fatigue, cognitive dysfunction, and disturbed sleep. Treatment for fibromyalgia should include a combination of nonpharmacologic and pharmacologic approaches. Patient education regarding the disease is important to provide a framework for understanding symptoms. The focus of treatment should not be on eliminating pain, but rather improving function and quality of life. Physical conditioning is an important part of improving function and should include a multifaceted exercise program with aerobic exercise, strength training, and exercises that incorporate relaxation techniques such as yoga or Tai Chi. Cognitive behavioral therapy can be useful in improving sleep disturbance and also in decreasing illness behaviors.

Pharmacologic therapy in fibromyalgia is targeted at the afferent and efferent pain pathways. The two most common categories of medications for fibromyalgia are antidepressants and anticonvulsants. Amitriptyline, duloxetine, and milnacipran have all been used with some efficacy in fibromyalgia. Duloxetine and milnacipran have been approved by the U.S.

Food and Drug Administration for the treatment of fibromyalgia. The anticonvulsants that are predominantly used in fibromyalgia are those that are ligands of the α-2-δ subunit of voltage-gated calcium channels. These include gabapentin and pregabalin, which are also FDA approved for treatment of fibromyalgia.

Anti-inflammatory medications and glucocorticoids are not effective in fibromyalgia. However, if there is a comorbid triggering condition such as rheumatoid arthritis, appropriate therapy directed at the underlying disorder is critical to controlling symptoms of fibromyalgia as well. Opioid analgesics such as oxycodone should be avoided. They have no efficacy in treating fibromyalgia and may induce hyperalgesia that can worsen both pain and function.

66. The answer is A.

(Chap. 22) Fibromyalgia is characterized by chronic widespread musculoskeletal pain, stiffness, paresthesia, disturbed sleep, and easy fatigability. It occurs in a 9:1 female-to-male ratio. It is not confined to any particular region, ethnicity, or climate. While the pathogenesis is not clear, there are associations with disturbed sleep and abnormal pain perception. Fibromyalgia is diagnosed by the presence of widespread pain, a history of widespread musculoskeletal pain that has been present for more than 3 months, and the presence of neuropsychological dysfunction (fatigue, waking unrefreshed, or cognitive symptoms). In the prior diagnostic criteria, it was required to demonstrate pain on palpation at 11 of 18 tender point sites. However, this was abandoned in the updated criteria because it was felt that strict application of a threshold of pain could lead to underdiagnosis of the disorder. Besides pain on palpation, the neurologic and musculoskeletal examinations are normal in patients with fibromyalgia. Psychiatric illnesses, particularly depression and anxiety disorders, are common comorbidities in these patients but do not help satisfy any diagnostic criteria.

67. The answer is A.

(Chap. 23) The finding shown in Figure 67 is characteristic of clubbing. Clubbing occurs in the distal portions of the digits and is characterized by widening of the fingertips, convexity of the nail contour, and loss of the normal 15° angle between the proximal nail and cuticle. Clinically, it sometimes can be difficult to ascertain whether clubbing is present. One approach to the diagnosis of clubbing is to measure the diameter of the finger at the base of the nail and at the tip of the finger in all 10 fingers. For each finger, a ratio between the base of the nail and the tip of the finger is determined. If the sum of all 10 fingers is greater than 1, then clubbing is felt to be present. A simpler approach is to have an individual place the dorsal surfaces of the distal fourth digits from each hand together. In a normal individual, there should be a diamond shaped space between the digits. When an individual has clubbing, this space is obliterated.

Clubbing most commonly occurs in advanced lung disease, especially bronchiectasis, cystic fibrosis, and interstitial lung diseases like sarcoidosis or idiopathic pulmonary fibrosis. Clubbing was originally described in individuals with empyema and can occur in chronic lung infections, including lung abscess, tuberculosis, or fungal infections. Pulmonary vascular lesions and lung cancer also are associated with clubbing. However, chronic obstructive pulmonary disease does not cause clubbing.

The causes of clubbing are not limited, however, to the pulmonary system alone. Clubbing can be a benign familial condition and is also associated with a variety of other disorders. This includes cyanotic congenital heart disease, subacute bacterial endocarditis, Crohn's disease, ulcerative colitis, celiac disease, and cancer of the esophagus, liver, small bowel, and large bowel. In untreated hyperthyroidism clubbing can occur in association with periostitis in a condition called thyroid acropachy. While these numerous clinical associations have been described for many centuries, the cause of clubbing remains unknown.

68. The answer is E.

(Chap. 24) Trochanteric bursitis is a common cause of hip pain and results from inflammation within the bursa that surrounds the insertion of the gluteus medius onto the greater trochanter of the femur. Bursae lie throughout the body with the purpose of facilitating movement of tendons and muscles over bony prominences. Bursitis has many causes including overuse, trauma, systemic disease, or infection. Trochanteric bursitis typically presents with acute or subacute hip pain with a varying quality. The pain localizes to the lateral aspect of the hip and upper thigh. Direct palpation over the posterior aspect of the greater trochanter reproduces the pain, and often sleeping on the affected side is painful. Pain is also elicited with external rotation and resisted abduction of the hip. Treatment of trochanteric bursitis includes the use of nonsteroidal anti-inflammatory medications and avoidance of overuse. If the pain persists, steroid injection into the affected bursa may be beneficial.

Other causes of hip pain include osteoarthritis, avascular necrosis, meralgia paresthetica, septic arthritis, occult hip fracture, and referred pain from lumbar spine disease. In patients with true disorders of the

hip joint such as osteoarthritis, avascular necrosis, and occult hip fracture, the pain is most commonly localized to the groin area. Meralgia paresthetica (lateral femoral nerve entrapment syndrome) causes a neuropathic pain in the upper outer thigh with symptoms ranging from tingling sensations to a burning pain. When degenerative spinal disease is the cause of referred hip pain, there is typically back pain as well. In addition, palpation over the lateral joint would not reproduce the pain. Iliotibial band syndrome causes lateral knee pain but not hip pain.

69. The answer is B.

(Chap. 24) The iliotibial band is comprised of thick connective tissue that runs along the outer thigh from the ilium to the fibula. When this band becomes tightened or inflamed, pain most commonly occurs where the band passes over the lateral femoral condyle of the knee, leading to a burning or aching pain in this area that can radiate toward the outer thigh. This overuse injury is most often seen in runners and can be caused by improperly fitted shoes, running on uneven surfaces, and excessive running. It is also more common in individuals with a varus alignment of the knee (bowlegged). Treatment of iliotibial band syndrome includes rest, NSAIDs, physical therapy, and addressing risk factors such as poorly fitted shoes or running on uneven surfaces. Glucocorticoid injection at the lateral femoral condyle may alleviate pain, but running must strictly be avoided for 2 weeks following injection. In refractory cases, surgical release of the iliotibial band may be beneficial.

70. The answer is A.

(Chap. 24) Adhesive capsulitis is characterized by pain and restricted motion of the shoulder. Usually this occurs in the absence of intrinsic shoulder disease, including osteoarthritis and avascular necrosis. It is, however, more common in patients who have had bursitis or tendinitis previously, as well as patients with other systemic illnesses, such as chronic pulmonary disease, ischemic heart disease, and diabetes mellitus. The etiology is not clear, but adhesive capsulitis appears to develop in the setting of prolonged immobility. Reflex sympathetic dystrophy may also occur in the setting of adhesive capsulitis. Clinically, this disorder is more commonly seen in females over age 50. Pain and stiffness develop over the course of months to years. On physical examination, the affected joint is tender to palpation, with a restricted range of motion. The gold standard for diagnosis is arthrography with limitation of the amount of injectable contrast to less than 15 mL. In most patients, adhesive capsulitis will regress spontaneously within 1–3 years. NSAIDs, glucocorticoid injections, physical therapy, and early mobilization of the arm are useful therapies.

71. The answer is A.

(Chap. 16) This patient presents with a multisystem illness involving the heart, kidneys, and peripheral nervous system. The physical examination is suggestive of amyloidosis with classic waxy papules in the folds of his body. The laboratory test results are remarkable for renal failure of unclear etiology with significant proteinuria but no cellular casts. A possible etiology of the renal failure is suggested by the elevated gamma globulin fraction and low hematocrit, bringing to mind a monoclonal gammopathy perhaps leading to renal failure through amyloid AL deposition. This could also account for the enlarged heart seen on the echocardiography and the peripheral neuropathy. The fat pad biopsy is generally reported to be 60% to 80% sensitive for amyloid; however, it would not allow a diagnosis of this patient's likely myeloma. A right heart catheterization probably would prove that the patient has restrictive cardiomyopathy secondary to amyloid deposition; however, it too would not diagnose the underlying plasma cell dyscrasia. Renal ultrasonography, although warranted to rule out obstructive uropathy, would not be diagnostic. Similarly, the electromyographic and nerve conduction studies would not be diagnostic. The bone marrow biopsy is about 50% to 60% sensitive for amyloid, but it would allow evaluation of the percent of plasma cells in the bone marrow and allow the diagnosis of multiple myeloma to be made. Multiple myeloma is associated with amyloid AL in approximately 20% of cases. Light chains most commonly deposit systemically in the heart, kidneys, liver, and nervous system, causing organ dysfunction. In these organs, biopsy would show the classic eosinophilic material that, when exposed to Congo red stain, has a characteristic apple-green birefringence.

72. The answer is B.

(Chap. 17) When patients present with proximal muscle weakness and myositis, whether polymyositis, dermatomyositis, or inclusion body myositis, the diagnosis is confirmed by analysis of serum muscle enzymes, EMG findings, and muscle biopsy. The most sensitive serum enzyme is creatinine kinase (CK), which can be elevated as much as 50-fold in active disease. CK levels usually parallel disease activity, but can be normal in some patients with inclusion body myositis or dermatomyositis. CK is always elevated in active polymyositis and thus is considered

most sensitive. Other enzymes may be elevated as well including glutamic-oxaloacetic transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, and aldolase.

73. The answer is C.

(Chap. 17) Various autoantibodies against nuclear antigens, e.g., ANAs, and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathies. The antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti–signal-recognition particles). The antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the antisynthetases and is clinically useful because up to 80% of patients with this autoantibody will have interstitial lung disease. Patients with anti-Jo-1 may also have Raynaud's phenomenon, nonerosive arthritis, and the MHC molecules DR3 and DRw52. Interstitial lung disease associated with anti-Jo-1 is often rapidly progressive and fatal, even if treated aggressively with cyclophosphamide or other immunosuppressants.

74. The answer is A.

(Chap. 17) Dermatomyositis is associated with malignancy in up to 15% of cases, thus age-appropriate cancer screening is indicated when this diagnosis is made. Exhaustive cancer searches are not recommended, however. Dermatomyositis may be associated occasionally with scleroderma and mixed connective tissue disease, but less frequently with systemic lupus erythematosus, rheumatoid arthritis, or Sjögren's syndrome, which are more closely associated with polymyositis or inclusion body myositis (IBM). Viruses may be associated with IBM and polymyositis, but are not proven to be associated with dermatomyositis. Parasites and bacteria such as cestodes and nematodes are associated with polymyositis, but not other forms of inflammatory myopathy. Finally, thyroid-stimulating immunoglobulins are not known to be associated with dermatomyositis.

75. The answer is A.

(Chap. 17) A common mistake in the management of patients with inflammatory myopathy is to "chase the CK" instead of adjusting therapy based on the clinical response. The goal of therapy is to improve strength. If that goal is being achieved, no augmentation of therapy is necessary. In this case, the plan to switch to long-term maintenance with steroid-sparing immunosuppressants should still be pursued. There have been no controlled studies comparing mycophenolate to methotrexate for long-term use in polymyositis, and in the absence of an adverse reaction to mycophenolate, therapy should not be changed. Despite an elevated CK, patients with polymyositis who are responding to therapy do not need a repeat muscle biopsy.

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